1-1-2017

# Patient Friendly Formulations Utilizing Hot Melt Extrusion Technology

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# PATIENT FRIENDLY FORMULATIONS UTILIZING HOT MELT EXTRUSION TECHNOLOGY

A Dissertation presented for the Doctor of Philosophy Degree

The University of Mississippi

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April 2017

# ABSTRACT

This research work exhibited the new outlook of hot melt extrusion technology for orally disintegrating tablet, fast disintegration films and fixed dose combinations. Previous research demonstrated these applications by conventional formulation techniques which has inherent shortcoming of use of large amount of solvent and batch size manufacturing. This present work addressed some of the unique challenges which could provide patients ease of administration and reduce dosing frequencies, and moreover, mitigate the manufacturing challenges.

For orally disintegrating tablet study, ethylcellulose, along with a suitable plasticizer, was used as a polymeric carrier. Pore forming agents were incorporated into the extruded matrix to enhance drug release. A modified screw configuration was applied to improve the extrusion processability and to preserve the crystallinity of the API. The milled extrudates were subjected to dissolution testing in an artificial salivary fluid and investigations using e-tongue, to assess the extent of masking of bitter taste of the API. There was an insignificant amount of drug released from the formulation in the salivary medium while over 80% of drug released within 30 min in 0.1 N HCl. ODTs were also developed with the extrudate mixed with mannitol and crospovidone. The quality properties such as friability and disintegration time of the ODTs met the USP specifications. The lead extrudate formulations and the ODTs prepared using this formulation were subjected to human gustatory evaluation. The formulations were found to mask the unpleasant taste of caffeine citrate significantly.

Additionally, melt extrusion provided peculiar advantages for oral fast disintegrating film development. Modified starch with glycerol was used as a polymer matrix for melt extrusion. Sweetening and saliva-simulating agents were incorporated to improve palatability and lower the disintegration time of film formulations. A standard screw configuration was applied, and the last zone of the barrel was opened to discharge water vapors, which helped to manufacture non-sticky, clear, and uniform films. The film formulations demonstrated rapid disintegration times (6–11 s) and more than 95% dissolution in 5 min. In addition, the films had characteristic mechanical properties that were helpful in handling and storage. An animal model was employed to determine the taste masking of melt-extruded films. The lead film formulation was subjected to a human panel for evaluation of extent of taste masking and disintegration.

The novel double extrusion approach was utilized for the development of fixed dose combination. For this study, carbamazepine and caffeine citrate were selected as model drugs, and hydroxypropyl methyl cellulose (HPMC), hydroxy propyl cellulose (HPC) and poly ethylene oxide (PEO) were as polymeric carriers. Standard screw design was used for first extrusion and modified screw design for second extrusion. Two step dissolution was performed on extrudated formulations which demonstrated significantly different release profile compared to single extrudated formulations. The solid-state characterizations confirmed the presence of drug in an amorphous form and could not find any chemical interaction. In addition, the FTIR-chemical imaging results showed the uniform distribution of drugs in double extrudated formulations.

# DEDICATION

*This work is dedicated to my family, friends and all my teachers*

# ACKNOWLEDGMENTS

I would like to express my deep and sincere gratitude to department chair and my advisor, Dr. Michael A. Repka for his support, patience and encouragement throughout my research work. His motivation and great help at all the time during my research helped me learn many aspects required to achieve high standards in research.

I would like to take this opportunity to express my sincere thanks to Dr. S. N. Murthy, Dr. Soumyajit Majumdar, and Dr. Samir A. Ross for accepting my request, spending their valuable time and providing valuable suggestions during my prospectus that I believe have improved my overall work. It was kind of Ms. Deborah P. King for helping me with all the departmental procedures and providing all the supplies required on time.

I owe a great thanks to my senior lab members for teaching me the research basics of our lab. I also thank all the present group members and all the graduate students of pharmaceutics and drug delivery department for their support in various projects.

I would like to acknowledge the help of Ms. Reena N Murthy and Dr. H N Shivakumar (Institute for Drug Delivery and Biomedical Research, Bangalore, India) for their support in Taste masking and Film evaluation studies.

I owe my greatest thanks to my mother (Rekha Pimparade), father (Bhagwan Pimparade) my brother (Sumit Pimparade), and sister-in-law (Sapna Pimparade) for all the support and encouragement. A special thanks to my friends Mr. Abhijeet Maurya, Mr. Harshul Sharma,

Mr. Anh Vo and Mr. Suprabh Singh for their great support. I sincerely acknowledge Ashland Inc., (Wilmington, DE) and other funding sources that made my Ph.D. work possible.

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# CHAPTER I

## Development of taste masked caffeine citrate formulations utilizing hot melt extrusion technology and *in vitro-in vivo* evaluations


## Abstract

The objective of this study was to develop caffeine citrate orally disintegrating tablet (ODT) formulations utilizing hot-melt extrusion technology and evaluate the ability of the formulation composition to mask the unpleasant bitter taste of the drug using *in vitro* and *in vivo* methods. Ethylcellulose, along with a suitable plasticizer, was used as a polymeric carrier. Pore forming agents were incorporated into the extruded matrix to enhance drug release. A modified screw configuration was applied to improve the extrusion processability and to preserve the crystallinity of the API. The milled extrudates were subjected to dissolution testing in an artificial salivary fluid and investigations using e-tongue, to assess the extent of masking of bitter taste of the API. There was an insignificant amount of drug released from the formulation in the salivary medium while over 80% of drug released within 30 min in 0.1 N HCl. ODTs were also developed with the extrudate mixed with mannitol and crospovidone. The quality properties such as friability and disintegration time of the ODTs met the USP specifications. The lead extrudate formulations and the ODTs prepared using this formulation were subjected to human gustatory evaluation. The formulations were found to mask the unpleasant taste of caffeine citrate significantly.

## 1. Introduction

Some active pharmaceutical ingredients (API's) are generally associated with unpleasant taste. The formulations containing such APIs are poorly accepted by patients and the adherence to treatment is adversely affected. Bad taste is a primary barrier while administrating drugs to children. For example, more than 90% of pediatricians reported that the taste and palatability were the greatest hurdles to complete treatment (Mennella et al., 2013). Therefore, it is necessary to discover robust approaches to formulate the dosage forms to mask the unpleasant taste of the API to improve the ease of administration and palatability (Jacqz-Aigrain and Choonara, 2006).

Traditionally, liquid type oral dosage forms incorporated with excess amounts of sweeteners is one of the common approaches to mask the unpleasant taste of APIs, particularly in pediatric medications. However, this type of formulation is associated with various shortcomings such as physical and chemical stability, use of alcohol and dose variability (Niazi, 2004). A World Health Organization (WHO) working document recommends refraining from incorporating coloring and flavoring agents in pediatric dosage forms (Susan and Walters, 2011). Thus, solid oral dosage forms become one of the more attractive choices for pediatricians and care takers as the usage of these excipients is less required in this case. Moreover, solid oral dosage forms tend to exhibit improved storage and transportation qualities in addition to more accurate dose precision (Strickley et al., 2008). However, in the context of pediatric populations, conventional tablets may be difficult to swallow and, therefore, present choking hazards. ODTs are a solid oral dosage form, which disintegrates very rapidly, typically within 30 seconds, with or without the administration of additional water. These are particularly convenient for people suffering from dysphagia, stroke, thyroid disorders, Parkinson's disease, multiple sclerosis and cerebral palsy (Badgujar and

Mundada, 2011).

Some common techniques for the development of taste masked solid dosage formulations are complexation (Dinge and Nagarsenker, 2008; Mahesh et al., 2010), freeze-drying (Seager, 1998), microencapsulation (Al-Omran et al., 2002; Shah et al., 2008a), fluidized-bed coating (Behzadi et al., 2008; Hamashita et al., 2008) and supercritical fluids (Benoit et al., 2000; Hanna and York, 2006). Recently, HME has demonstrated its utility in the development of taste masked formulations (Gryczke et al., 2011; Maniruzzaman et al., 2012a) by using a physical barrier between bitter drugs and taste receptors. Hot-melt extrusion (HME) is a viable technology for processing pharmaceutical formulations as it is potentially a single step and continuous process, which helps to decrease the formulation steps. HME has become a well established pharmaceutical processing technique over the last two decades. It is primarily employed for solubility improvement, but has also shown considerable utility for various usages such as controlled release formulations and targeted drug delivery including taste masking systems (Maniruzzaman et al., 2012b; Maniruzzaman et al., 2013).

HME processing involves the physical mixing of a formulation at elevated temperatures, and pressure(s) while also being under high shear. Nakamichi et al demonstrated that the kneading paddles play an important role in changing the crystallinity and dissolution characteristics of a solid dispersion (Nakamichi et al., 2002). Formulations containing a poorly soluble API require more aggressive screw designs, which include multiple mixing zones along with other screw elements (Figure. 1-1a). This design tends to impart improved solubility, which translates to improved bioavailability for BCS II APIs (Deng et al., 2013; Mohammed et al., 2012).

However, the specific screw design is dictated by the particular properties that are desired in the final product, which is determined on a case-by-case basis. The physical transformation of the drug from the crystalline to the amorphous state is responsible for the improvement in dissolution. However, sometimes it is favorable to retain the crystalline form to avoid excess release of a highly soluble drug in short time periods for controlled release formulations or improvement in the stability of BCS class II drug solid dispersions (Reitz et al., 2012).

Caffeine citrate is a bitter, white crystalline and highly water soluble API, which is classified as a BCS class I drug (Wu and Benet, 2005). Caffeine citrate is a central nervous stimulant and helps to restore alertness. Pharmaceutically, caffeine citrate is used in the treatment of apnea in newborns; also it is the component of many of the analgesic formulations, where it demonstrates a synergistic effect with those analgesics (Comer et al., 2001; Sawynok, 1995).

The main purpose of this study was to develop a robust formulation to mask the bitter taste of a model API, caffeine citrate, by a hot-melt extrusion process and evaluate the taste masked effects with *in vitro* and *in vivo* methods. In this work, the authors employed multiple techniques, including a human taste panel, dissolution and e-tongue analysis in a single study.

## 2. Materials and methods

### 2.1. Material

Caffeine Citrate (CC), Calcium Carbonate, Calcium Phosphate and Triethyl citrate (TEC) were purchased from Fisher Scientific (Pittsburgh PA, USA). Magnesium oxide USP light was ordered from PCCA (Houston, TX, USA). AqualonTM Ethylcellulose N7 (EC) Polyplasdone™ (grades XL and XL-10) was supplied by Ashland Specialty Ingredients (Wilmington, DE, USA).

Magnesium stearate was purchased from Spectrum Chemical Mfg. Corp (Gardena, CA, USA), Pearlitol® 50C-mannitol was supplied by Roquette America Inc (Keokuk, IA, USA).

2.2. Preparation of melt extrudate formulations

Caffeine citrate (20% w/w) was blended with EC, triethyl citrate (TEC) and with or without pore formers in an amount outlined in Table 1-1 using a V-shell blender (GlobePharma, Maxiblend, New Brunswick, NJ, USA) after passing through ASTM #30 mesh. The blends were melt-extruded using a co-rotating twin-screw extruder (11 mm Process 11, ThermoFisher Scientific, Pittsburgh, PA, USA) with a modified screw design at 50 rpm over a temperature range of 125–130°C. The extrudate was milled using a comminuting mill (Fitzpatrick, Model "L1A", Elmhurst, IL, USA) and sieved through an ASTM # 40/35. The portion retained by an ASTM # 35 sieve was stored in foil lined polyethylene bags for further analysis and processing.

2.3. Thermogravimetric analysis (TGA)

Thermogravimetric analysis studies (Perkin Elmer Pyris 1, Shelton, CT, USA) were performed to estimate the thermal stability of the API and excipients during HME processing. The data was analyzed using Pyris software. The API and excipients were heated from 30 – 200°C at 20°C/min.

2.4. Differential scanning calorimetry (DSC)

DSC studies were performed with a Perkin Elmer Diamond differential scanning calorimeter (DSC) equipped with Pyris software (Shelton, CT, USA). Samples were prepared by sealing 3-5 mg of pure API, physical mixtures and milled extrudates in hermetically sealed

aluminum pans and heated from the temperature range of 30°C to 180°C at the heating rate of 20°C/min under an inert nitrogen atmosphere at a flow rate of 20 mL/min.

**Table 1-1:** HME Formulations

| Formulations (%w/w) | CC1 (control) | CC2 | CC3 | CC4 | CC5 | CC6 | CC7 | CC8 | CC9 | CC10 | CC11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Caffeine Citrate | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| TEC | 5 | 5 | -- | -- | 10 | 10 | 5 | 5 | 5 | 5 | 5 |
| Stearic acid | -- | -- | 5 | 5 | -- | -- | -- | -- | -- | -- | -- |
| Mannitol | -- | 3 | -- | 3 | -- | 3 | 5 | 10 | -- | -- | -- |
| Calcium Carbonate | -- | -- | -- | -- | -- | -- | -- | -- | 15 | -- | -- |
| Magnesium Oxide | -- | -- | -- | -- | -- | -- | -- | -- | -- | 15 | -- |
| Calcium Phosphate | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 15 |
| Aqualon™ Ethyl Cellulose (ECN7) | 75 | 72 | 75 | 72 | 70 | 67 | 70 | 65 | 60 | 60 | 60 |

2.5. Fourier transforms infrared spectroscopy (FTIR)

FTIR spectra of the API, polymer, physical mixtures and milled extrudates were recorded using an Agilent Cary 660 FTIR spectrophotometer (Santa Clara, CA, USA) to investigate any possible interactions between the drug, polymer and other excipients.

2.6. Analytical method

A Waters High performance liquid chromatography (HPLC) system equipped with a Water 600 binary pump, Waters 2489 UV/detector, and Waters 717 plus autosampler (Waters Technologies Corporation, 34 Maple St., Milford, MA 0157) and a Phenomenex Luna 5um C18 (2) 250 x 4.6 mm column (Torrance, CA, USA) were used at a detection wavelength of 273 nm. The mobile phase consisted of Methanol and water at a ratio of 70:30 (v/v). The mobile phase flow rate was maintained at 1.0mL/min. and an injection volume of was 20 μL was used(O'connell and Zurzola, 1984). HPLC data was analyzed using Empower V. software (Milford, MA, USA).

2.7. *In vitro* dissolution studies

*In vitro* dissolution studies were performed by a modified dissolution method, as currently there are no regulatory (USP or FDA) guidelines available to evaluate taste masked formulations in salivary dissolution media. Briefly this study was conducted using 500 mL of salivary media with expeditious sampling points to mimic the oral environment and to minimize the handling and sampling error, which could arise in low volume salivary dissolution.

Dissolution studies were performed on the milled extrudates and ODTs using USP apparatus I (50 rpm) in 500mL of artificial salivary fluid adjusted to pH 6.8 for oral drug release (Azarmi et al., 2007) (Table 1-2). The samples were analyzed at 5 second intervals using a

Rainbow Dynamic Dissolution Monitor® System powdered by Indigo™ software (Pion Inc., Billerica, MA, USA). Gastric drug release was assessed in 900 mL of 0.1 N HCl using USP apparatus I (50 rpm). The gastric release samples were analyzed by HPLC. In both instances the dissolution temperature was maintained at 37 ± 0.5°C using a Hanson SR8-Plus dissolution testing system (Chatsworth, CA).

**Table 1-2:** Artificial saliva dissolution media (pH 6.8)

| Compound | Concentration (g/L) |
|---|---|
| CaCl2·2H2O | 0.228 |
| MgCl2·6H2O | 0.061 |
| NaCl | 1.017 |
| K2CO3·1.5H2O | 0.603 |
| Na2HPO4·7H2O | 0.204 |
| NaH2PO4·H2O | 0.273 |

2.8. Evaluation using E-Tongue

An Astree e-tongue system equipped with an Alpha M.O.S sensor set # 2 (composed of 7 specific sensors, ZZ, AB, BA, BB, CA, DA, JE; Alpha MOS America, Hanover, MD, USA) was employed. The conditioning step was performed using 0.01 N HCl to hydrate the sensors and assess for noise or drift. After the instrument passed the conditioning step, the E-tongue was calibrated in 0.01 N HCl with reference to the manufacturer's specified set of target values and margin of error (Siddiqui et al., 2013). After calibration, hydrochloric acid, sodium chloride and methyl sodium glutamate were utilized to check the discrimination of sour, salty and umami tests by the sensors.

Approximately 0.05 g of sample was dispersed in 50 mL of phosphate buffer solution (pH 6.8) and gently shaken for 30 seconds. The suspension was filtered with a 0.45 micron syringe filter (nylon membrane) into a 25 mL beaker and the acquisition time was set at 120 seconds

(Maniruzzaman et al., 2012a; Siddiqui et al., 2013). Ten samples for each run were required per manufacturer's guidelines.

2.9. Preparation of Orally Disintegrating Tablets (ODTs)

The extrudates prepared as discussed in Section 2.2 were blended with mannitol, used as a diluent, and Polyplasdone™ XL or XL-10, used as a disintegrant (Table 1-3) utilizing a V-shell blender. Magnesium stearate was added when two minutes of blending remained. The final blend was evaluated for bulk & tap density as well as moisture content.

The ODTs were prepared by direct compression on a Globe tablet press (MCTMI, Globe Pharma Inc. (New Brunswick, NJ, USA) using 10 mm standard concave tooling at a compression force of 5–10 kN.

2.10. Evaluation of Compressibility

Carr's Index (Compressibility Index I) and Hausner's ratio of ODT formulation blends with magnesium stearate were calculated by measuring the tapped bulk and poured bulk volume of powders after subjecting to 100 taps in a graduated cylinder.

2.11. Quality of ODTs

Tablet hardness, weight variation and average thickness were measured using a Smart Test 50 (Sotax Corporation, Westborough, MA, USA) and disintegration time was evaluated using Disi Test 20 (Sotax Corporation, Westborough, MA, USA) disintegration tester filled with simulated salivary fluid which was thermally equilibrated to 37±0.5°C prior to testing. Friability studies were performed using a dual scooping projection Vankel type Drum (Model 10801, Vankel Industries

Inc. Edison, NJ, USA) for 4 minutes at 25 rpm.

### 2.12. Human taste evaluation

Taste masking evaluation was performed at the Institute for Drug Delivery and Biomedical Research, Bangalore India (Protocol number VIPS/2013/12). The subjects were recruited after obtaining informed consent. The study is also in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

#### 2.12.1. Human subject selection criteria

Nine human subjects belonging to either sex were recruited. They were asked to abstain from coffee/tea and other beverages for 12 hours. The subjects were only allowed to drink water for the 12 hours. Moreover, they were asked not to eat chocolate or other candy for over 6 hours. Inclusion criteria was healthy human subjects of age 18-42 and exclusion criteria was subjects suffering from fever, smokers, mouth ulcers, dry mouth, cold, nose block and wounds.

#### 2.12.2. Data collection

Before data collection the subjects were asked to wash their mouth with ambient temperature water. The surface temperature of the tongue was recorded using an IR thermometer and difference of ±5°C compared to body temperature was considered an exclusion criteria.

##### 2.12.2.1. Bitterness perception

The subjects were asked to taste aqueous solutions of CC starting from a very dilute solution escalating to higher concentrations by placing 2 ml of solution for 30 seconds on the

tongue/buccal cavity. The concentrations screened were 0, 0.5, 1, 5, 10 and 40 mg. The volunteers were asked to report the following perception each time as 1- I feel bitter taste, 2- I feel something but cannot identify the taste, and 3-I do not feel the taste.

The subjects who answer 2 or 3 were asked to taste higher concentration solution until they expressed perception 1. This was recorded as the threshold for an individual. The individuals who reported a score of 1 at least 1/5th the drug concentration of the actual dose were only allowed to test the product.

Above the individual's perception threshold, a few higher concentration API solutions were made for tasting by the subjects and they were subsequently asked to provide a score for each of the solutions (Table.1-4). The highest concentration of solution contained caffeine citrate equivalent to the dose present in the tested products. The scoring pattern was followed according to modified hedonic scale where 0- no taste, 1-threshold, 2-slightly bitter, 3-moderately bitter, 4-bitter and 5-strongly bitter.

2.12.2.2 Formulation evaluation and data analysis

A washout interval of 12-24 hours was allowed after screening the standard solution. The individuals were asked to taste the products (physical mixture, hot-melt extruded formulation or ODT) randomly (blinded) and asked to score the product. The products were wetted with water (0.5 ml) and placed on the tongue/buccal cavity for a duration of 30 – 40 seconds and asked to score the bitterness on a scale of 0-5 for each product. Sufficient washout time was allowed between the products and allowed to drink copious amounts of water after tasting each product.

The scores given by all individuals was averaged and expressed as mean standard deviation. The mean scores between the physical mixture and formulation was compared using a

student t-test at 95% confidence level and $P<0.05$ was considered statistically significant.

## 3. Results and Discussion

### 3.1. Preparation of hot-melt extrudates utilizing modified screw configuration

Ethyl cellulose is a suitable polymer for HME due to its thermoplastic property, however it can be a challenge to process due to a thermally narrow processing window. EC has a high glass transition temperature (129-133°C), while thermal processing above 150°C induces slight color changes due to oxidation and degradation (Ashland, 2002). These limitations, a narrow processing window and hydrophobicity obstruct, can be resolved using processing and formulation approaches through low shear screw configurations, compatible plasticizers and pore forming agents.

EC, proved difficult to extrude using the standard screw configuration (Figure 1-1a) as a result of the three mixing zones therein. Additionally, caffeine citrate is a highly soluble drug and the employment of this configuration resulted in the complete conversion of crystalline caffeine citrate to the amorphous form, which will result in rapid drug release in the oral cavity and further hinder taste masking efficiency. Therefore, for this study a modified screw design (Figure 1-1b), which could apply sufficient mixing without complete conversion of caffeine citrate into the amorphous phase, was utilized. Using a combination of approaches such as incorporation of plasticizer and a modified screw configuration, helped to extrude within a thermal processing window with very low torque, successfully producing white extrudates without any color change and nor degradation of API or polymer.

**a)**

**b)**

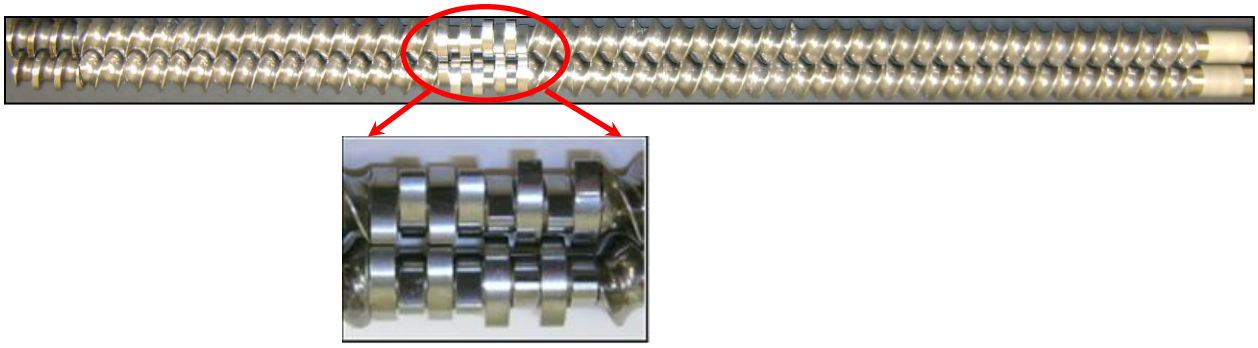


**Figure 1-1.** Twin screw extruder screws; (a) for high shear, (b) for low shear and its magnified image of the kneading zone

3.2. Physiochemical properties of hot-melt extrudates

DSC, TGA and FTIR were performed to determine the thermal stability at the extrusion conditions and the post extrusion physical characterization of the extrudates, respectively. The thermal stability of the drug, polymer and excipients was determined using TGA. All of the materials utilized for these studies showed no appreciable level of weight loss at the extrusion temperatures used (Figure 1-2).

DSC studies were conducted to evaluate the physical state of the drug in the polymer matrix. Pure caffeine citrate (CC) exhibited a sharp endothermic peak onset at 168°C shown in Figure 1-3. while EC exhibited an absence of a melting peak, which confirmed the complete amorphous nature of ethylcellulose (thermogram not shown). DSC thermograms of all of the

extrudates illustrated a shifting of the endothermic peak associated with caffeine citrate, which may be due to the incorporation of TEC (as a plasticizer). Formulations with TEC and mannitol 3%, 5% and 10% showed a decrease in the melting temperature of CC. Additionally, with an increase in the concentration of mannitol, the peak became shifted and broadened due to the very close melting point of caffeine citrate and mannitol. Formulations CC9 and CC11 with calcium carbonate and calcium phosphate showed a shifting of the sharp endothermic peak; however, the formulation CC10 with magnesium oxide resulted in a very weak melting peak due to partial solubilization of caffeine citrate during extrusion. Also, this result confirmed TEC's role as a suitable plasticizer for EC which helped to reduce the glass transition temperature (Tg) and melt viscosity due to an increase in the free volume of the ethyl cellulose chain (Crowley et al., 2004).

Any significant quantity of a compound in which intermolecular interactions are present, hydrogen bonding for example, contains numerous interacting species, each of which would be involved in the interactions to varying extents. Therefore, what should be evident in the event of an intermolecular interaction would be a broadening of the spectral region in question, as the resulting spectrum is an average of these individual responses. Similarly, this broadening of the spectral region would result in a shift in the peaks center, which is represented by Figure 1-4. This is evident in neither the physical mixtures nor the extruded formulations. To the contrary, what is evident in the spectra is not a broadening of the spectral bands, nor a shift in the peaks center, but a very narrow and sharp response from the ethyl cellulose hydroxyl moiety near $2972^{cm-1}$, which is indicative of a lack of hydrogen bonding. This region is of particular interest as it is the only region with hydrogen bonding potential on the polymer chain that is not subject to steric hindrance. Likewise, the numerous potential hydrogen bond acceptors/donors available on caffeine citrate are neither broadened nor shifted, but exhibit a marked decrease in intensity resulting from the API's

dilution in the carrier. This indicates that the taste masking properties of the extruded formulations are due solely to physical entrapment of the API in the hydrophobic carrier.

Thermal stabilities of all of the excipients were established and the DSC investigations confirmed the presence of crystalline caffeine citrate in all of the extrudates. Hence, these data affirmed the effectiveness of a modified screw design to retain the physical state of the drug during the extrusion process. FTIR data proved the absence of interaction(s) of drug with carrier or other excipients during HME.

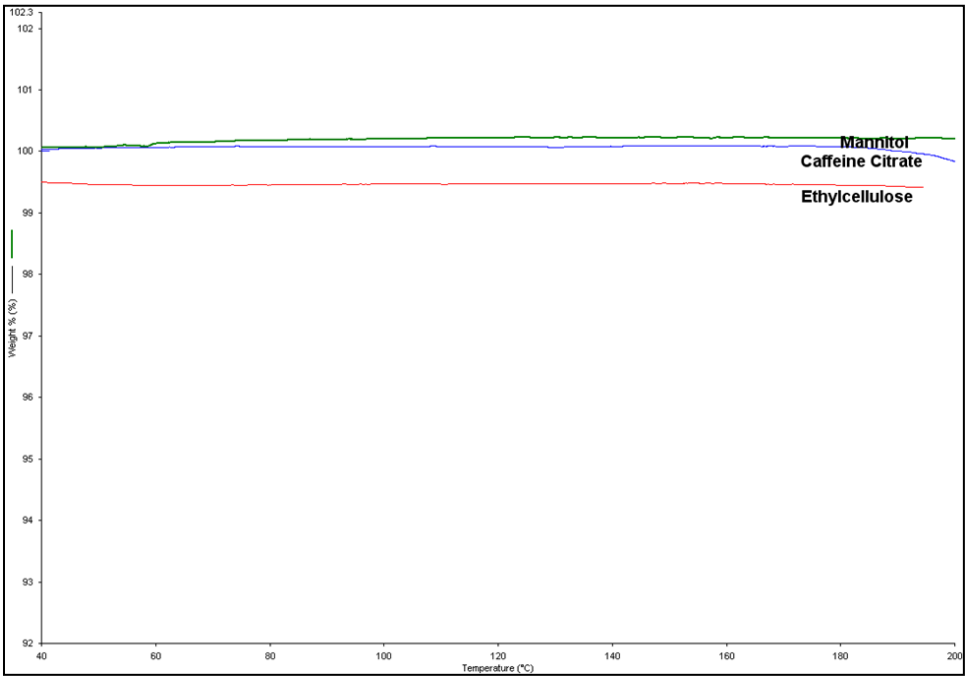



**Figure 1-2.** TGA Thermograms of Mannitol, caffeine citrate and Ethyl cellulose

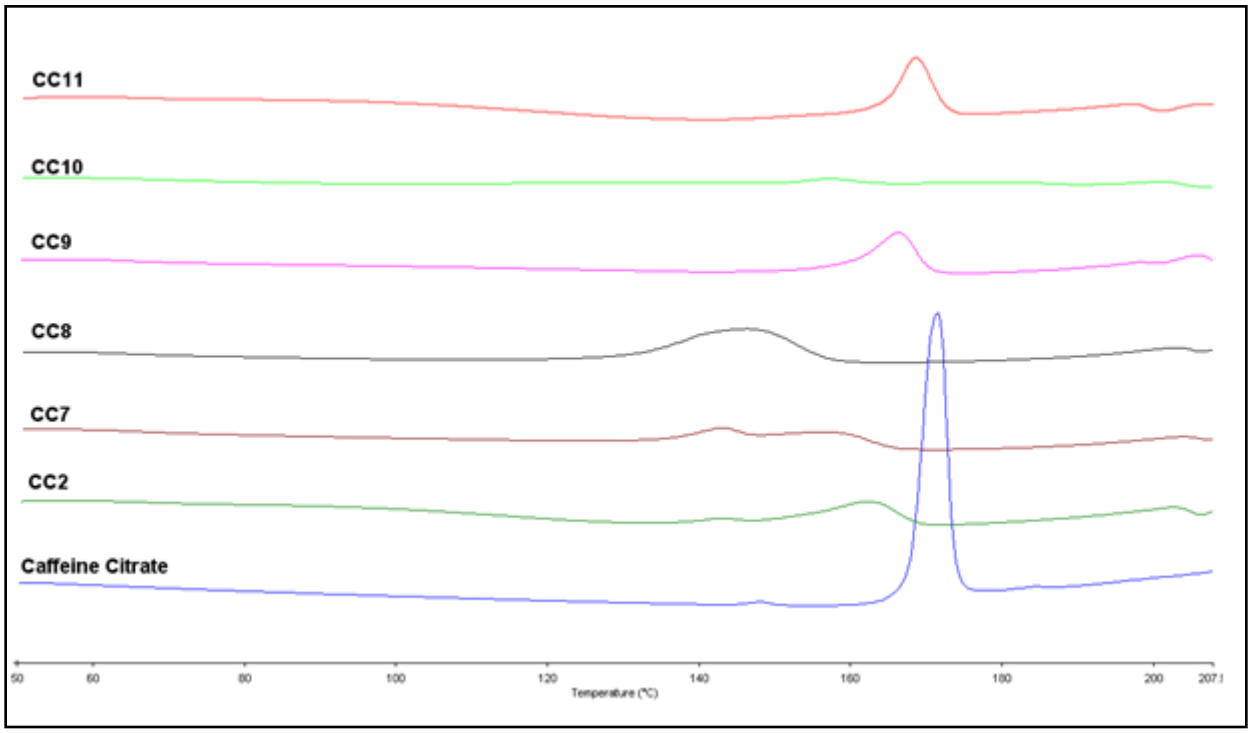



**Figure 1-3.** DSC Thermograms of extruded formulations and caffeine citrate; (CC2) caffeine citrate with EC/TEC and 3%mannitol, (CC7) 5%mannitol, (CC8) 10%mannitol, (CC9) 15% calcium carbonate, (CC10) 15% magnesium oxide, (CC11) 15%calcium phosphate.

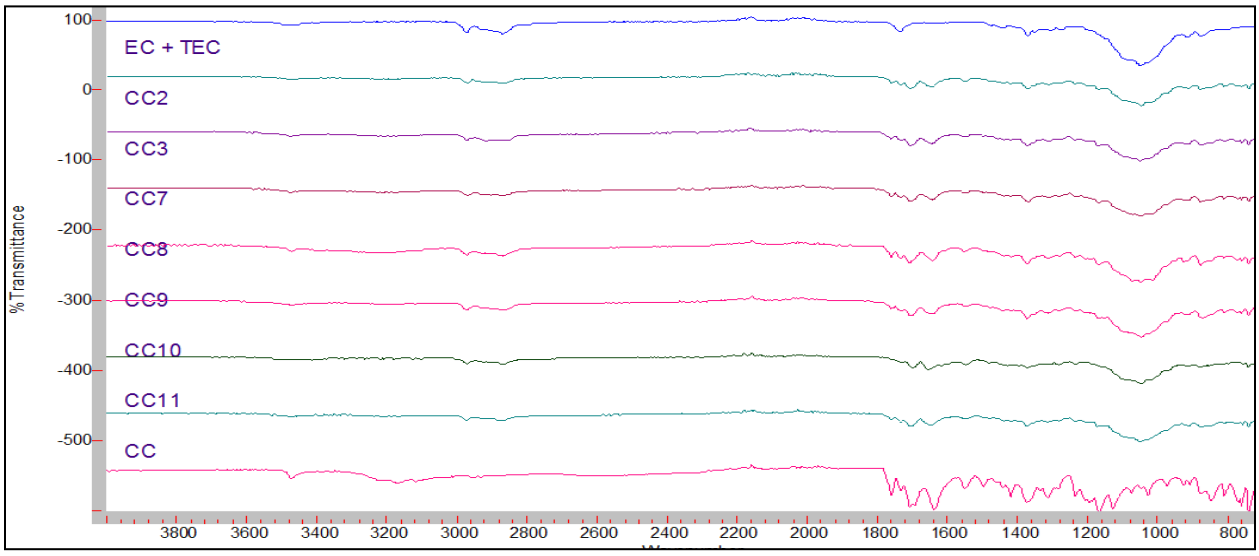



**Figure 1-4.** FTIR spectra of extrudates; (CC) caffeine citrate, (CC2) with 3%mannitol, (CC7) with 5%mannitol, (CC8) with 10%mannitol, (CC9) with 15%calcium carbonate, (CC10) with 15% magnesium oxide, (CC11) with 15%calcium phosphate.

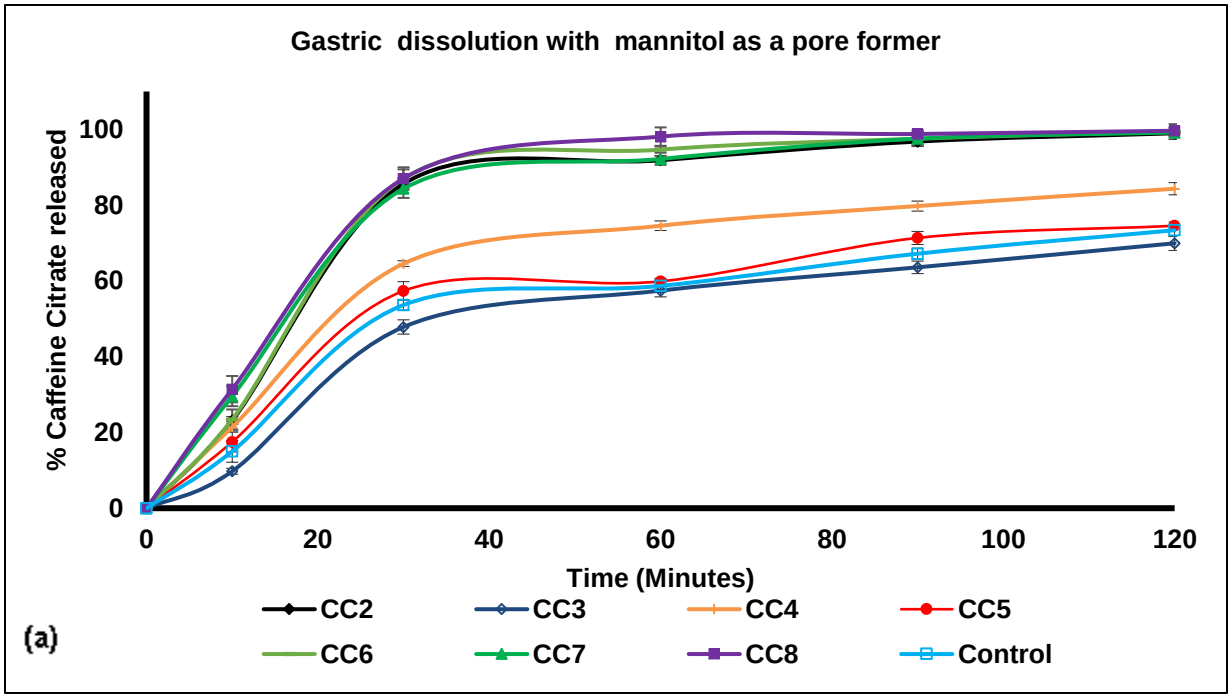
3.3. Dissolution studies and the role of pore forming agents

Ethyl cellulose (EC) is one of the most widely explored polymers for the formulation of microencapsulations, controlled release matrix systems, taste masking, as well as solvent extrusion granulations. EC has acceptable properties for taste masked formulations, however due to its considerable hydrophobicity, it cannot be employed for taste masked immediate release formulations. Therefore, it is necessary to incorporate release modulators or pore forming agents to assist in more rapid drug diffusion from the carrier (Mohammed et al., 2012). These agents could allow rapid entry of dissolution media into the matrix, which ultimately leads to rapid drug release. This type of sugar alcohols are highly water soluble compounds, and at higher loadings in a formulation may undesirably increase the release of the drug in oral cavity. Thus, the use of pH dependent pore formers is suitable for taste masked formulations as well as subsequent gastric release. With this in mind, calcium carbonate, calcium phosphate and magnesium oxide were selected as they are soluble in an acidic environment (Lai et al., 2013), which circumvents drug release in the mouth while allowing rapid gastric release.

Dissolution profiles with pore formers showed an appreciable change in the rate and extent of release in 0.1 N HCl. Formulations without pore formers showed around 50% release in 30 minutes (Figure 1-5a). However, while some pore formers improve drug release in the gut, some may also improve drug release in the oral cavity, which is to the detriment of taste masking. Therefore, the selection of an appropriate pore former is critical to obtain a balance of oral cavity release and gastrointestinal release. For this study, we evaluated a water soluble sugar alcohol mannitol and pH dependent inorganic salts calcium phosphate, calcium carbonate and magnesium oxide. Formulations CC2, CC7 and CC8 with 3, 5 and 10% mannitol (Figure 1-5a) improved the release to more than 80% in 30 minutes and more than 92% in 60 minutes. On the other hand,

formulations CC10 and CC11 with 15% of magnesium oxide (MgO) and calcium phosphate ((Ca)2PO4 ) exhibited 75% release in 30 minutes (Figure 1-5b) and above 90% in 60 minutes. CC9 with 15% calcium carbonate demonstrated 72% release in 30 minutes and approximately 75% in 60 minutes. The release mechanism of caffeine citrate in the ethyl cellulose matrix can be explained in that when a matrix is composed of a hydrophilic drug and hydrophobic polymer, the drug release occurs by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network. As drug release continues, the interconnecting cluster increases the pore network through which interior drug clusters can diffuse (Crowley et al., 2004). Despite this interconnecting cluster, the drug dissolution was not sufficient to obtain the targeted release profile without pore formers.

Formulation CC3 and CC4 with stearic acid as a plasticizer without and with 3% mannitol as a pore former, CC5 and CC6 with 10% TEC as a plasticizer without and with 5% mannitol did not demonstrate relevant results with the aim of this project so the results are not discussed in detail.



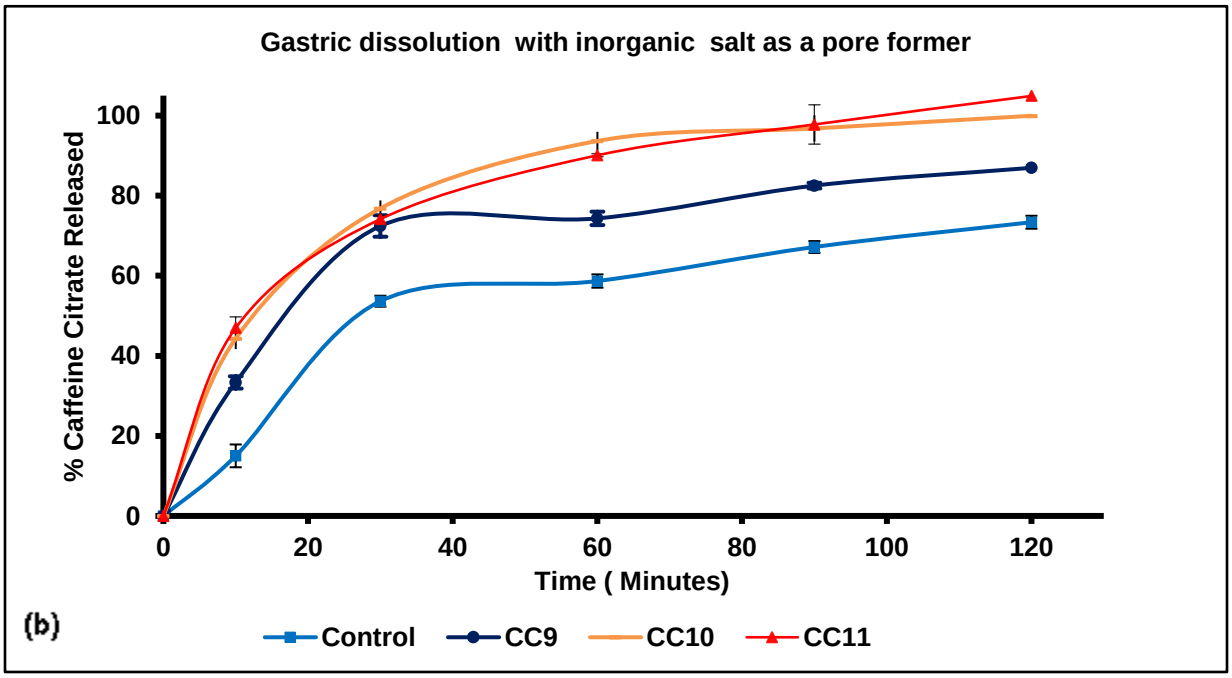




**Figure 1-5.** Dissolution profiles of caffeine citrate in EC/TEC extrudates (n=3); (a) gastric dissolution profile with mannitol as pore former, control (CC1) caffeine citrate with EC/TEC, (CC2) with 3%mannitol, (CC7) with 5% mannitol, (CC8) with 10% mannitol; (b) gastric dissolution profile with inorganic salts, (CC9) caffeine citrate with EC/TEC and 15%calcium carbonate, (CC10) with 15% magnesium oxide, (CC11) with 15% calcium phosphate.

3.4. *In vitro* -Taste masking evaluations

Dissolution testing using artificial salivary media (pH 6.8) was used as a primary screening method for taste masking ability of the formulation. The outcome as shown in Figure 1-6a and 1-6b from this concise study helped to understand the release behaviors which were extrapolated to oral release of formulations.

Successful formulations which showed low drug release in salivary fluid were evaluated using e-tongue where the outputs of these e-tongue studies were analyzed using a principal component analysis (PCA) where bitterness of the formulations was evaluated based on the distance between placebo and samples. The greater the proximity of samples to placebo, the more efficient the taste masking property was presumed to be. For this study, we evaluated ten samples from each beaker and used data from five samples (the first 3 and last 2 readings values were disregarded). This method helped to reduce an intra-sample variance, which is a common shortcoming of the electronic tongue that has been previously reported in the literature (Lorenz et al., 2009; Rahman et al., 2012; Siddiqui et al., 2013).

As it can be seen in Figure 1-6a and 1-6b, the amount of caffeine citrate released in CC2 with 3% mannitol in the EC/TEC matrix was around 2% in 30 seconds in artificial saliva whereas the formulation CC7 and CC8 with 5% and 10 % mannitol showed more than 13% in same amount of time. On the other hand, the release profile of formulations with inorganic salts, CC9, CC10 and C11, showed less than 3% release under the same conditions.

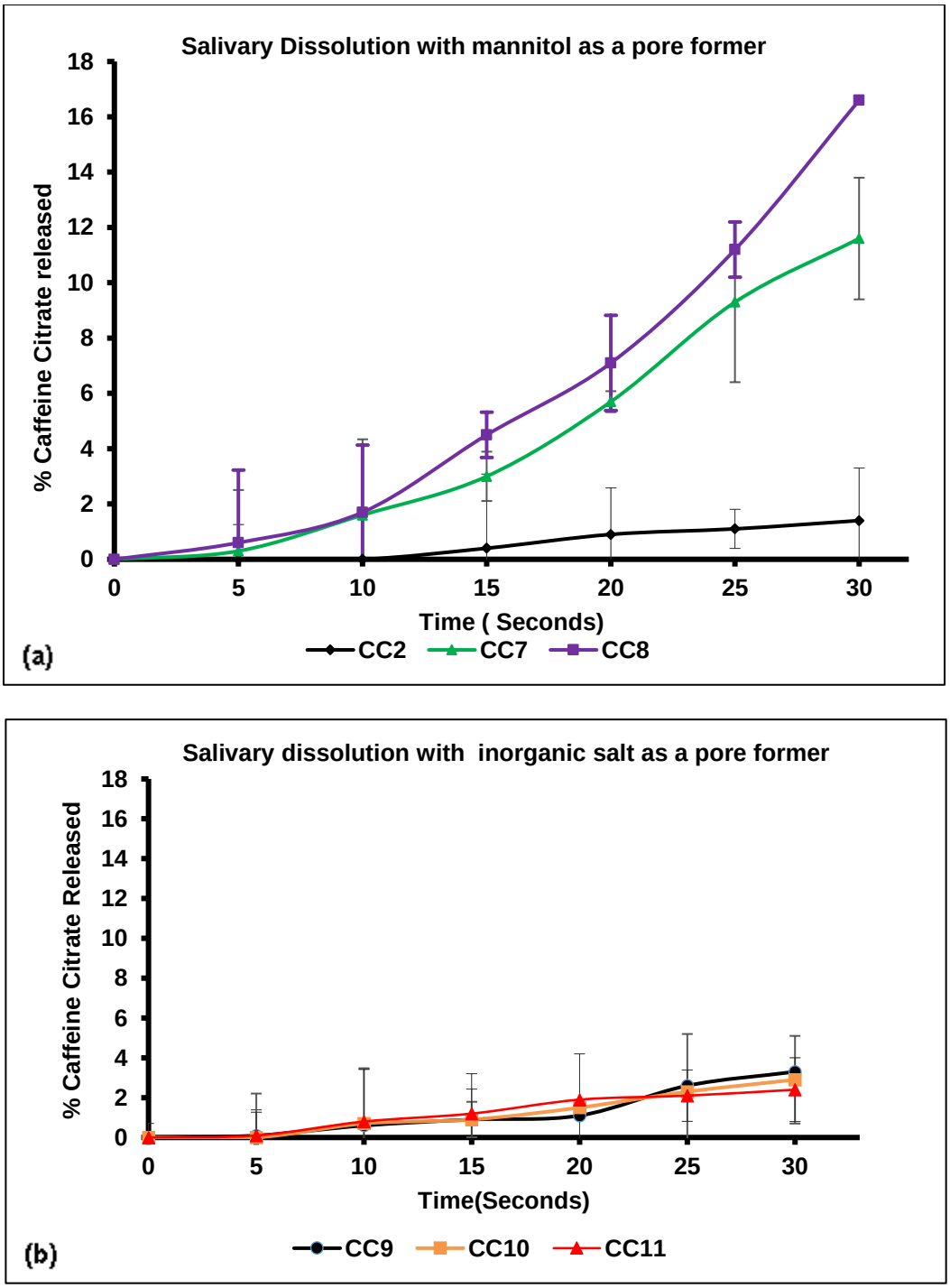
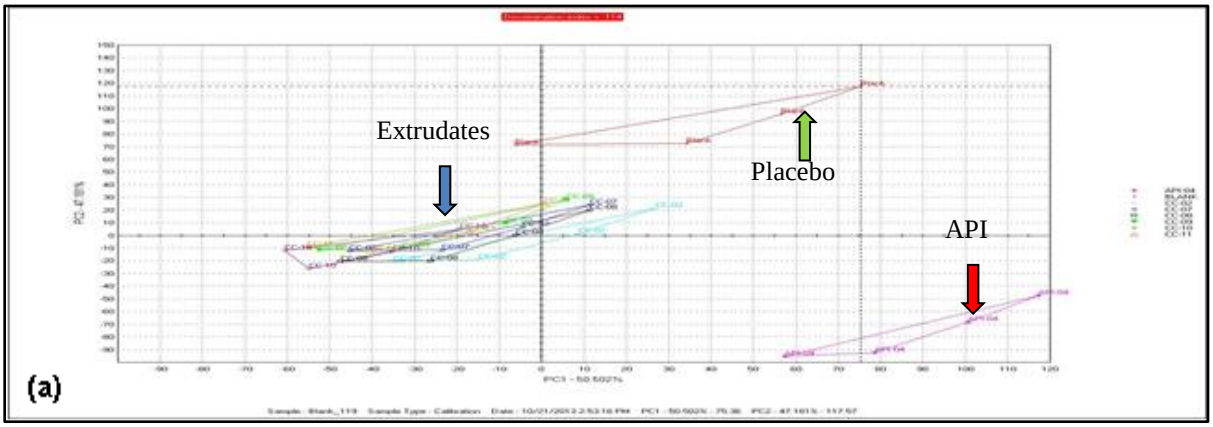



**Figure 1-6.** Salivary dissolution profiles of caffeine citrate in EC/TEC extrudates (n=3); (a) dissolution profile with mannitol: (CC2) with 3% mannitol, (CC7) with 5% mannitol, (CC8) with 10% mannitol; (b) dissolution profile with inorganic salts, (CC9) with 15% calcium carbonate, (CC10) with 15% magnesium oxide, (CC11) with 15% calcium phosphate.

As illustrated in Figure 1-7a and 1-7b, the blank solution is at close distance with the extruded formulations. All of the formulations CC2, CC7 and CC8 with mannitol as a pore former had almost the same distance from the blank which confirmed the use of mannitol in the range of 3-10% without compromising the perceived taste. Formulations CC9, CC10 and CC11 with inorganic salts as a pore formers showed slightly better taste masking efficiency when compare to formulations with mannitol. More precisely, these inorganic pore formers only dissolve at acidic pH, which confirmed their importance in taste masking formulations. Formulations with magnesium oxide as a pore former exhibited a closer proximity to the blank compared to formulations with calcium carbonate and calcium phosphate.

Based on these findings from drug release profiles and e-tongue taste masking evaluations, the behaviors of low amounts of mannitol and organic salts as pore formers were very appropriate in a hydrophobic matrix such as ethylcellulose. These findings warranted studies of the taste masking effects in the mouth as well as evaluation of drug release in gastric fluid.



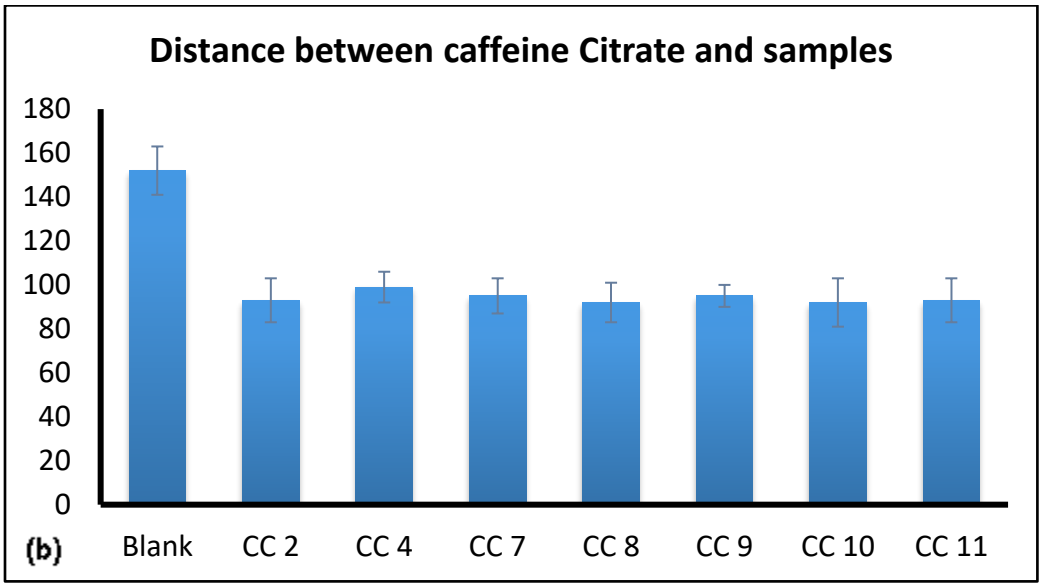



**Figure 1-7.** Taste masking evaluation using Astree e-tongue; (a) PCA chart for E-tongue results, (b) bar graph of distance between placebo and formulations

3.5. Preparation and Characterization for ODTs

The optimized extrudates which showed excellent taste masking were selected to develop an ODT according to FDA's industrial guidelines (CDER, 2008). The caffeine citrate and EC extrudates with water soluble or insoluble pore formers were blended with super-disintegrates, Polyplasdone™ XL or XL-10, and mannitol as a diluent. ODT compositions in this study are provided in Table 1-3.

Before tablet compression, all tablet blends were evaluated for Hausner's ratio and Carr's index (Figure. 1-8), which were less than 1.12 and 11, respectively. Both these parameters are the most common indicators of the flowability of a powder blend. Hausner's ratio of < 1.11 indicates good flowability whereas > 1.60 indicates poor flowability. Values between 1.12 and 1.18 is considered to be of acceptable flowability (Shah et al., 2008b). It is common to consider that the

smaller the Carr's index, the better the flowability. For example, values <10 indicate excellent, 11-15 good, 16 - 20 fair and > 26 poor flow (Shah et al., 2008b). In summary, all of the powder blends utilized for tableting demonstrated good flowability. For large scale tablet manufacturing processing, flowability is a critical parameter which determine the flow of powder from hopper to dies and it may affect content uniformity, weight and hardness of the tablet if the flowability is poor(Shah et al., 2008b). This results confirmed that the improvement in flowability and compressibility is mainly attributed to the use of EC in extrusion and mannitol as a diluent in the tablet blend.

Most of the studies revealed that a higher concentration of super-disintegrates affect disintegration time (DT) and hardness adversely. Thus, the optimized concentration is very important to obtain the DT below 30 seconds. In preliminary studies, formulations without super-disintegrates delayed disintegration time, which confirmed the importance of Polyplasdone™ XL and XL10 as a critical component for ODT disintegration (Results not shown). Moreover, with increasing the amount of super-disintegrates up to 5% showed an improvement in hardness, however with an increase in concentration above 10% exhibited lower hardness and increased disintegration time (Results not shown). These results are in agreement with a previously published study (Gryczke et al., 2011).

As per our study, the appropriate super-disintegrant concentration was found to be 5%, which showed the DT of 14 -19 seconds, which is less than the FDA's guideline of 30 seconds (Figure. 1-9). The mechanism involved in the Polyplasdone™ XL and XL10 behavior for good DT was due to the rapid wicking of water into their porous particle size morphology. This generates rapid volume expansion by increasing the hydrostatic pressure that causes rapid tablet disintegration (Gryczke et al., 2011). All the tablets produced using HME had low hardness values

(3.6- 3.9 kp); however, the friability was less than the acceptable range as it was measured to be below 1% in optimized formulations.

All the ODT formulations showed very similar gastric dissolution release profiles as that of extrudates (results not shown). During compression of tablets, extrudates maintained their integrality and did not change dissolution behavior. The overall outcome was the robust, taste masked and very rapidly disintegrating ODT formulations with acceptable friability.

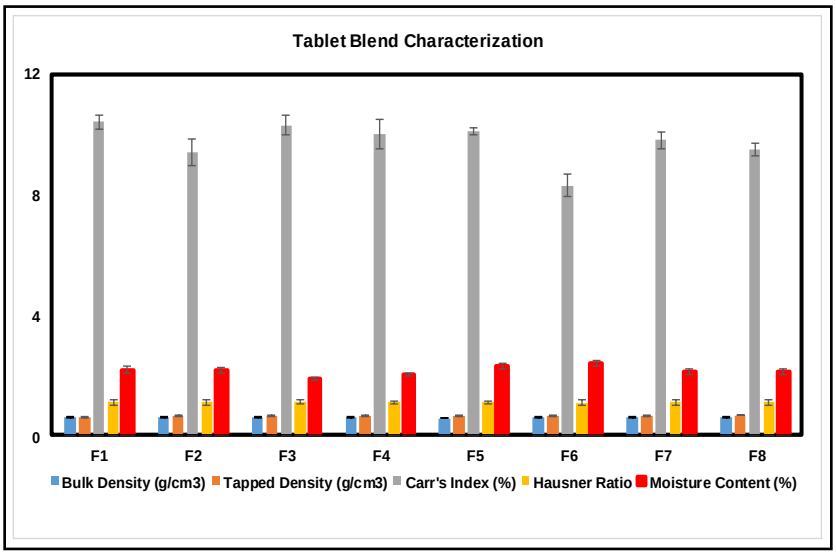



**Figure 1-8.** Schematic diagram of tablet blend characterizations, (F1) CC2 extrudates and polyplasdone XL, (F2) CC2 extrudates and polyplasdone XL-10, (F3) CC9 extrudates and polyplasdone XL, (F4) CC9 extrudates and polyplasdone XL-10, (F5) CC10 extrudates and polyplasdone XL, (F6) CC10 extrudates and polyplasdone XL-10, (F7) CC11 extrudates and polyplasdone XL, (F8) CC11 extrudates and polyplasdone XL-10.

**Table 1-3**: Composition of ODT formulations

| ODT Formulations (% w/w) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| CC2 Extrudates | 50 | 50 | -- | -- | -- | -- | -- | -- |
| CC9 Extrudates | -- | -- | 50 | 50 | -- | -- | -- | -- |
| CC10 Extrudates | -- | -- | -- | -- | 50 | 50 | -- | -- |
| CC11 Extrudates | -- | -- | -- | -- | -- | -- | 50 | 50 |
| Mannitol | 44.5 | 44.5 | 44.5 | 44.5 | 44.5 | 44.5 | 44.5 | 44.5 |
| Polyplasdone XL | 5 | -- | 5 | -- | 5 | -- | 5 | -- |
| Polyplasdone XL-10 | -- | 5 | -- | 5 | -- | 5 | -- | 5 |
| Magnesium Stearate | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

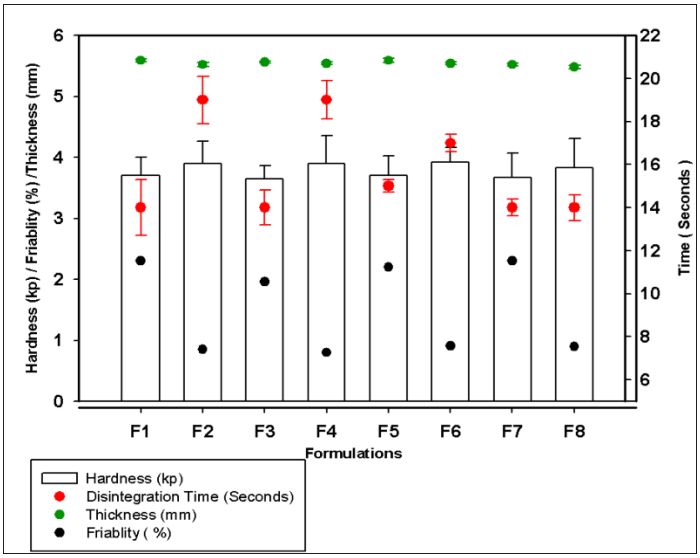



**Figure 1-9.** Schematic diagram of ODT characterizations; (F1) CC2 extrudates and polyplasdone XL, (F2) CC2 extrudates and polyplasdone XL-10, (F3) CC9 extrudates and polyplasdone XL, (F4) CC9 extrudates and polyplasdone XL-10, (F5) CC10 extrudates and polyplasdone XL, (F6) CC10 extrudates and polyplasdone XL-10, (F7) CC11 extrudates and polyplasdone XL, (F8) CC11 extrudates and polyplasdone XL-10.

3.6. Evaluation of taste of the products in human volunteers

Taste evaluation was carried out with 9 healthy volunteers. Initially bitterness perception of each volunteer was assessed using different concentrations of API in 2 ml aqueous solution to understand sensitivity of each human subject to the API. Three subjects had bitterness thresholds at 0.5 mg, four subjects had a threshold at 1.0 mg and the remaining two subject's threshold were 5.0 mg. As stated in Table 1-4, a dose of 5.0 mg or above indicated very high bitterness and only three volunteers could tolerate 40 mg solution of CC. Thus, this initial evaluation confirmed that the volunteers are appropriate to test the melt extruded products containing caffeine citrate.

Based on the taste evaluation using artificial salivary dissolution and e-tongue, formulations CC2 with 3% mannitol and CC11 with 15% calcium phosphate as a pore former were selected to reaffirm the outcome using a human taste panel. Results shown in Figure 1-10, the

physical mixture of CC2 exhibited the unacceptable and intolerable bitterness in all of the human subjects (an average score of 4.6 on a scale of 1-5), it confirmed that the amount of mannitol and EC did not aid to minimize the bitterness produced due to caffeine citrate. When the milled extrudates were administrated, the average response dropped considerably (an average score of 2 on a scale of 1-5) and statistical analysis of taste responses confirmed a significant difference in bitter taste ($p<0.0006$) between the CC2 physical mixture and CC2 extrudates. Moreover, the results of formulation CC11 was comparable to that of CC2, where the average score for physical mixture was ~5; however the milled extrudates was only ~2.6 which, indicated the effectiveness of the extruded formulations compared to its physical mixture. The taste masking effectiveness of CC11 vs. its corresponding the physical mixture proved to be statistically significant ($p<0.003$). Remarkably, this result from human subjects has corresponded to e-tongue results as well as artificial saliva dissolution data. This outcome has demonstrated that the use of *in vitro* studies such as e-tongue and artificial saliva dissolution could be applicable to ascertain the taste masked efficiency of the formulations.

In addition, HME technology proved the taste masking efficiency of formulations with an EC matrix and selected pore formers. This taste test for bitterness also indicated that the amount and type of pore former were critical factors for the development of taste masked formulations using hydrophobic polymeric matrices. Comparison of physical mixtures with extrudates affirmed the significance of the HME process and also proved the dilution of caffeine citrate is not adequate for producing taste masked formulations. These data asserted the theory of entrapment of CC in within the EC matrix incorporated via HME and its role to hinder the release in the oral cavity. The pH dependent and independent pore former type and concentration supported their importance without affecting the taste, as most of the pore formers facilitate release in the oral cavity.

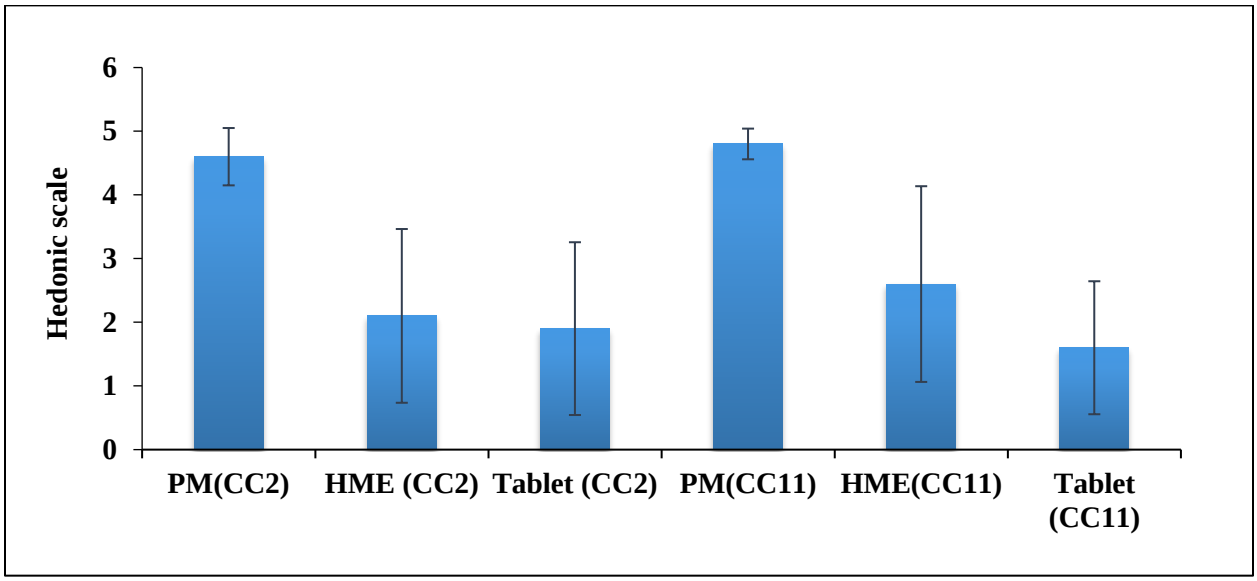



**Figure 1-10.** Human taste panel evaluations; PM (CC2): pre-extrusion blend caffeine citrate with EC/TEC and 3%mannitol, HME (CC2): hot melt extrudate of CC2, Tablet CC2: ODT of CC2; PM(CC11): pre extrusion blend caffeine citrate with EC/TEC and 15% calcium phosphate, HME(CC11): hot melt extrudate of CC11, Tablet CC11: ODT of CC11.

**Table 1-4**: Human taste perception response

| Amount of API/2ml | Volunteers | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| 0 mg | | | | | | | | | |
| 0.5 mg | | | | | | 1 | 1 | | 1 |
| 1.0 mg | 1 | | 1 | | 1 | 4 | 3 | 1 | 2 |
| 5.0 mg | 2 | 1 | 4 | 1 | 3 | 5 | 4 | 4 | 4 |
| 10.0 mg | 4 | 2 | 5 | 5 | 5 | | 5 | 5 | 5 |
| 40.0 mg | 5 | 4 | 5 | | | | | | |

## 4. Conclusion

This study demonstrated the effectiveness of an ethyl cellulose matrix with a pore former for the development of taste-masked formulations. To facilitate the processability of the high Tg of the ethylcellulose matrix, and to preserve the crystallinity of the model API, the screw configuration was modified to reduce the shear imparted during processing coupled with the incorporation of a plasticizer to decrease the Tg. Strikingly, the results from salivary dissolution and e-tongue data were in good correlation with the human taste panel. The development of taste-masked formulations required an appropriate processing technique, such as hot melt extrusion that could entrap the drug forming a barrier to achieve a palatable taste as well as demonstrating controlled release. This formulation could be used as a platform for unpleasant tasting, highly soluble drugs. In summary, the final ODTs were robust, taste masked dosage forms, adhering to acceptable ODT guidelines.

# CHAPTER II

## Development and Evaluation of an Oral Fast Disintegrating Anti-allergic Film using Hot-melt Extrusion Technology


## Abstract

The main objective of this novel study was to develop chlorpheniramine maleate orally disintegrating films (ODF) using hot-melt extrusion technology and evaluate the characteristics of the formulation using *in vitro* and *in vivo* methods. Modified starch with glycerol was used as a polymer matrix for melt extrusion. Sweetening and saliva-simulating agents were incorporated to improve palatability and lower the disintegration time of film formulations. A standard screw configuration was applied, and the last zone of the barrel was opened to discharge water vapors, which helped to manufacture non-sticky, clear, and uniform films. The film formulations demonstrated rapid disintegration times (6–11 s) and more than 95% dissolution in 5 min. In addition, the films had characteristic mechanical properties that were helpful in handling and storage. An animal model was employed to determine the taste masking of melt-extruded films. The lead film formulation was subjected to a human panel for evaluation of extent of taste masking and disintegration.

# 1. Introduction

It is estimated that 26–50% of the patient population find difficulty in swallowing tablets and hard gelatin capsules (Andersen et al., 1995). These patients mainly include the elderly who have difficulty taking conventional oral dosage forms because of hand tremors and dysphagia, and pediatric patients who are often fearful of taking solid oral dosage forms owing to their underdeveloped muscular and nervous systems (Slowson and Slowson, 1985). In addition, patients who are mentally ill, developmentally disabled, uncooperative, on reduced liquid-intake plans or nauseated, and travelers who may not have access to clean water also are candidates for ODFs (Chang et al., 2000; Lindgreen and Janzon, 1993).

The traditional alternative to swallowing difficulties is formulating a drug substance in liquid dosage form. However, liquid dosage forms have several limitations, such as the need for measuring, bulkiness, physical, chemical, and microbial stability issues, spoilage, inaccurate dosing, and organoleptic properties of drug and drug formulations (Shahiwala, 2011).

Conventional solid oral formulations contributed significantly to minimizing the shortcomings of liquid dosage forms. The crushing of tablets or opening of capsules is a straightforward way for patients or caregivers to lessen the swallowing difficulties. However, serious consequences may be associated with modified-release, enteric-coated, and cytotoxic or hormonal medicines, as these formulations are designed for special cases (Wright, 2002). Moreover, European Medical Agency does not recommend the splitting or crushing of tablets because the active pharmaceutical ingredient (API) is not evenly distributed in the tablet (Shah et al., 2010; Zhao et al., 2010). Thus, it is very convenient to develop a formulation that disintegrates in the oral cavity and eases the swallowing process.

In recent years, fast disintegrating oral formulations established their importance in patient population suffering from dysphagia, stroke, thyroid disorder, Parkinson's disease, multiple sclerosis, and cerebral palsy (Badgujar and Mundada, 2011). Commercially available orodispersible tablets (ODT) and orodispersible films (ODF) are the most successful platforms for pharmaceutical product development. ODTs are solid oral dosage forms that disintegrate rapidly, typically within 30 s, with or without the administration of additional water (Pimparade et al., 2015). They provided great comfort to patients with swallowing difficulties (Slavkova and Breitkreutz, 2015). Despite the benefits of ODTs, there are some challenges in their processing and handling owing to their fragility and brittleness, which warrant special package for protection during storage and transportation (Dahiya et al., 2009). The films are flexible and not as fragile as most ODTs. Hence, there is ease in transportation, consumer handling, and storage of ODFs.

ODF can be defined as a dosage form that employs a water-soluble polymer (generally a hydrocolloid, which may be a bioadhesive polymer), which allows the dosage form to quickly wet, adhere, and dissolve to release the drug when placed on the tongue or in the oral cavity (Shahiwala, 2011). ODF alleviated patient discomforts associated with swallowing disabilities without compromising the therapeutic effect. In addition, it could ease the administration of drugs to pediatric patient population (Reiner et al., 2010). Moreover, ODF can be helpful in curtailing dose variations in younger patients, in whom liquid formulations are the most accepted way of drug delivery.

Currently, solvent casting methods are commonly employed to produce ODFs, owing to its ease of production and low set up costs (Dixit and Puthli, 2009; Low et al., 2013a). Despite its wide application, products with batch-to-batch variation may be produced because of multiple steps involved in the production. In addition, air entrapment in the films is commonly observed in

solvent casting methods, which leads to dose variations and inappropriate esthetic appearance of the product (Low et al., 2013a). The use of large amounts of solvent is one of the biggest shortcomings of this method as solvent removal and disposal is a long and tedious process. Thus, it is very beneficial to develop a solvent-free, quick, and continuous process that could diminish the shortcomings of the current manufacturing method.

Hot melt extrusion (HME) is a one-step, solvent-free continuous manufacturing process, which established itself in the pharmaceutical arena for the development of various solid oral formulations (Albers et al., 2009; Almeida et al., 2011; Crowley et al., 2007; Desai et al., 2013; Feng et al., 2016; Forster et al., 2001; Morott et al., 2015; Repka et al., 2007; Vo et al., 2016; Vo et al., 2017). This technology involves the use of temperature and shear to process polymer blends and extrude them through a die of the desired design (Just et al., 2013). HME could be an effective alternative to the solvent casting method as it diminishes the inherent shortcomings, such as the use of solvents and problems involved in the mixing and drying steps. This ultimately makes HME process efficient and cost effective for patients (Hoffmann et al., 2011; Preis et al., 2013).

This study has three main objectives: to 1) develop a robust patient-friendly orally fast disintegrating film of chlorpheniramine maleate (CPM); 2) evaluate these formulations with different *in vitro* and *in vivo* techniques, and 3) demonstrate the feasibility of HME techniques for continuous manufacturing of ODF without the use of solvents. To the best of our knowledge, there is no published literature on the manufacturing of orally fast disintegrating formulations using HME technology and evaluation of films using *in vitro* and *in vivo* techniques.

## 2. Materials and Methods

### 2.1. Materials

CPM was purchased from MP Biomedicals, LLC (Solon, OH, USA). Lycoat® RS 780 (modified starch) was supplied by Roquette America Inc. (Keokuk, IA, USA). Citric acid and glycerol were ordered from Fisher Scientific (Pittsburgh PA, USA). Magnasweet® sample was gifted by Mafco worldwide LLC (Camden, NJ, USA). Sucralose was supplied by JK Sucralose Inc. (Edison, New Jersey, USA).

### 2.2. Thermal analysis

Thermogravimetric analysis (TGA) studies (Perkin Elmer Pyris 1, Shelton, CT, USA) were performed to estimate the thermal stability of the API and excipients during HME processing. Data were analyzed using Pyris software. The API excipients were heated from 30–160℃ at 20℃ /min.

### 2.3. Material preparation and blending

CPM, citric acid, and Lycoat® RS 780 were dry mixed at amounts outlined in Table 2-1 using a V-shell blender (GlobePharma, Maxiblend, New Brunswick, NJ, USA) after passing through an ASTM #30 mesh. The plasticizer (glycerol with dissolved sucralose and Magnasweet®) was incorporated slowly into a high-shear mixer (Model RSI 3VG, Robot Coupe Industrial Division, Ridgeland, MS, USA) containing the previously mixed blend with all excipients and allowed to blend for 10 min.

2.4. Hot melt extrusion

The blends were melt-extruded using a co-rotating twin-screw extruder (16 mm Prism EuroLab, ThermoFisher Scientific, Pittsburgh, PA, USA) at 30–50 rpm over a temperature range of 100–110℃. A degassing port was introduced in the last zone of the barrel to release excess water vapor, which would otherwise produce unwanted bubbles in the films. Additionally, the film die was installed with preset thickness. The physical blend of the formulation was manually fed into the hopper, and the films were collected, wrapped in wax paper, sealed, and stored in polyethylene bags at 25℃ with 40% relative humidity.

**Table 2-1:** HME formulations

| Formulation (%w/w) | Temperature (°C) | Sucralose | Magnasweet | Citric acid | CPM | GLY | Lycoat 780 | Screw speed (rpm) |
|---|---|---|---|---|---|---|---|---|
| N 1 | 100 | 0.5 | 0.5 | 4 | 5 | 20 | 70 | 50 |
| N 2 | 110 | 0.5 | 0.5 | 4 | 5 | 17 | 73 | 30 |
| N 3 | 100 | 0.5 | 0.5 | 6 | 5 | 17 | 71 | 50 |
| N 4 | 110 | 0.5 | 0.5 | 6 | 5 | 20 | 68 | 30 |
| N 5 | 100 | 0.5 | 0.5 | 4 | 10 | 20 | 65 | 30 |
| N 6 | 110 | 0.5 | 0.5 | 4 | 10 | 17 | 68 | 50 |
| N 7 | 100 | 0.5 | 0.5 | 6 | 10 | 17 | 66 | 30 |
| N 8 | 110 | 0.5 | 0.5 | 6 | 10 | 20 | 63 | 50 |
| N 9 | 105 | 0.5 | 0.5 | 5 | 7.5 | 18.5 | 68 | 40 |

## 2.5. Film characterizations

### 2.5.1 Film thickness and mechanical properties

The mechanical properties of the films were evaluated using the TA.XTPlus texture analyzer equipped with 5 kg load cell (Texture Technologies, Scarsdale, NY, USA). The films were cut into dumbbell shaped specimens with a width and length of 1.55 and 15.5 mm, respectively, and placed longitudinally in tensile grip probe on the texture analyzer. The films were tested at a crosshead speed of 2 mm/min and held between two clamps positioned at 5 mm. The results of film samples that broke at and not between the clamps were not included in the calculations. Each film formulation was measured with ten replicates (Low et al., 2013b). The tensile strength (Ts) and percent elongation (%E) were calculated using the results from texture analyzer. Film thickness was measured using an electronic caliper (Fisher Scientific, Pittsburgh, PA, USA) at different positions.

### 2.5.2 Disintegration test

The film was cut into an appropriate size as per the dose (4 mg) and placed in a petri dish. Then, 100 µL artificial salivary media was added, and the time for complete disintegration of the film was recorded (n =10).

### 2.5.3 Surface pH of film

The film was moistened using 5 µL water and a contact electrode touched the surface of the film (Oakton™ pH meter, Fisher Scientific, Pittsburgh, PA, USA), followed by pH measurement (n=6).

2.6. Analytical method

A Waters® high performance liquid chromatography (HPLC) system equipped with a Water® 600 binary pump, Waters® 2489 UV/detector, and Waters® 717 plus autosampler (Waters Technologies Corporation, Milford, MA, USA), and a Phenomenex Luna® 5 µm C18 (2) 250 x 4.6 mm column (Torrance, CA, USA) were used at a detection wavelength of 254 nm. The mobile phase consisted of 7.5 mM monobasic potassium phosphate in methanol and water at a ratio of 62.5:37.5 (v/v). The mobile phase flow rate was maintained at 1.0 mL/min, and an injection volume of 10 µL was used (Moyano et al., 2005). HPLC data were analyzed using Empower 2 software (Milford, MA, USA).

2.7. *In vitro* dissolution studies

The films for dissolution studies were cut into sizes relative to the dose of CPM (4 mg). The drug profile was evaluated using a USP dissolution apparatus-I (Hanson SR8, Chatsworth, CA) maintained at 37 ± 0.5℃ and having a shaft rotation speed of 100 rpm. The dissolution test was performed using 900 mL phosphate buffer (pH 6.8). The samples were withdrawn at 5, 10, and 30 min and analyzed using the HPLC- UV system.

2.8. X-ray diffraction studies (XRD)

X-Ray diffraction (Bruker D8 Advance, Madison, MI, USA) was used to determine the physical state of the drug, excipients, and film formulations. The X-ray diffraction apparatus used CuK radiation at 40 mA, 40 kV, a scanning speed of 2°/min, and diffraction angle (2θ) range of 5–55.

2.9. Scanning electron microscope (SEM)

The surface morphology of the films was evaluated using SEM analysis. The samples were mounted on adhesive carbon pads placed on aluminum and sputter coated with gold using a Hummer sputtering system (Anatech Ltd, Springfield, VA, USA) in a high vacuum evaporator. A JEOL JSM-5600 SEM operating at an accelerating voltage of 10 kV was used for imaging.

2.10. *In vivo* taste evaluation

Twenty-one naïve adult male Sprague-Dawley rats (175–200 g) were ordered from Harlan Laboratories (Houston, TX, USA) for the study. The rats were housed in Plexiglass cages with Corncob bedding in a vivarium that maintained a 12 h light/dark cycle and an ambient temperature of ~22°C. Food and water were available without any restriction, except during the training and taste evaluation experiments as mentioned below (2.10.1). All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at The University of Mississippi, University, USA (protocol no. 15-026). This study was performed as per the procedure in our previous publication on taste assessment method for bitter drugs (Tiwari, 2015).

2.10.1. Training paradigm

The rats were trained for licking behavior (response to thirst) by depriving them of water for 22 h, but they had ad libitum access to food. After the water deprivation period, the Plexiglass cage was divided using plastic transparent dividers to provide an individual water bottle to each animal. Eventually, the rats were provided with graduated water bottle for 30 min, and the amount consumed at 15 and 30 min were recorded. This training paradigm was performed for 2 days before the taste evaluation experiment.

2.10.2. Evaluation of bitterness sensitivity of rats

To determine the concentration of CPM for this study, a sensitivity test for bitterness was performed in rats. After depriving the rats of water for 22 h, sensitivity toward 0.5 mg/mL CPM solution was evaluated on the first day, followed by a washout period of 24 h. Subsequently, the effect of 1 mg/mL CPM solution was examined, and the results were recorded.

2.10.3. Experiment

The experiment was performed for 30 min with 30 mL test formulation following the 22 h water deprivation period. After each experiment, the rats had a washout period of 24 h to avoid any memory of the taste of the previous formulation. The rats had *ad libitum* access to food during the experiment and washout period. The amount of solution remaining at 15 and 30 min was noted and subtracted from the original test volume. Varying results caused by spilling of the test solution while measuring or leaking of bottle knob were omitted from the study. Notably, animal behavior responses such as jaw smacking, oral grooming, and retreating were observed, which was not the focus of this study. Formulations N2, N7, and N9 at 0.5 mg/mL CPM were used for bitterness evaluation study in rat model. The average amount of solution consumed by all animals was calculated and expressed as the mean standard deviation. The mean scores between the physical mixture and formulation were compared using a student t-test at 95% confidence level and $P<0.05$ was considered statistically significant.

2.11. Film evaluation by human panel

The evaluation of film for palatability, disintegration time (DT), and organoleptic

characteristics was performed at the Institute for Drug Delivery and Biomedical Research, Bangalore India (Protocol number VIPS/2013/12). The subjects were recruited after obtaining informed consent. This study is also in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The experimental procedure for this study was as per our previously published work (Juluri et al., 2016; Pimparade et al., 2015).

### 2.11.1. Human subject selection criteria

Six human subjects belonging to either sex were recruited. They were asked to abstain from coffee/tea and other beverages for 12 h. The subjects were allowed to drink only water for 12 h. Moreover, they were asked not to eat chocolates or other candies for over 6 h. The inclusion criterion was healthy human subjects aged 18-42 years, and the exclusion criteria were subjects suffering from fever, mouth ulcers, dry mouth, cold, nose block, and wounds as well as smokers.

### 2.11.2. Data collection

Before data collection, the subjects were asked to wash their mouth with water at ambient temperature. The surface temperature of the tongue was recorded using an infrared (IR) thermometer, and a difference of ±5℃ relative to the body temperature was considered an exclusion criteria.

#### 2.11.2.1. Bitterness perception

The subjects were asked to taste aqueous solutions of CPM, beginning with very dilute solutions and progressing to higher concentrations, by placing 2 mL solution for 30 s on the tongue/buccal cavity. The concentrations screened were 0, 0.5, 1, 2.5, and 4 mg. The volunteers

were asked to report the perception each time: 1- I feel bitter taste, 2- I feel something but cannot identify the taste, and 3-I do not feel the taste. The subjects who reported 2 or 3 were asked to taste higher concentrations of the solution until they expressed perception 1. This was recorded as the threshold for an individual. For individuals who reported a score of 1, at least 1/5th the drug concentration of the actual dose was only allowed for testing the products. A few high concentration API solutions above the individual's perception threshold were made for tasting, and the subjects were subsequently asked to provide a score for each solution (Table 2-3). The highest concentration of the solution contained CPM equivalent to the dose present in the products tested. The scoring pattern followed was according to modified hedonic scale: 0-no taste, 1- taste something (threshold), 2-slightly bitter, 3-moderately bitter, 4-bitter, and 5-strongly bitter.

2.11.2.2. Formulation evaluation and data analysis

A washout interval of 12–24 h was allowed after screening the standard solution. The individuals were asked to taste the products (physical mixture or ODF) randomly (blinded) and score the product. The products were placed on the tongue/buccal cavity for 30–40 s, and the subjects were asked to score the bitterness on a scale of 0–5 for each product. Moreover, volunteers were asked to report the time for complete disintegration of the film. Sufficient washout time was allowed between the products, and the volunteers were allowed to drink copious amounts of water after tasting each product. The average of the scores given by all individuals were taken and expressed as the mean standard deviation. The mean scores between the physical mixture and formulation were compared using a student t-test at 95% confidence level, and $P<0.05$ was considered statistically significant.

## 3. Results and Discussion

### 3.1. Preparation of hot-melt extruded film

Modified starch is very difficult to extrude because of its high glass transition temperature. Thus, there is a need to introduce a plasticizer during extrusion, which could reduce the melt viscosity and increase the free volume of starch chains. For this study, glycerin was used as a plasticizer in different proportions, and it exhibited excellent extrudability with significantly lower torque (4.8–7.2 Nm) values than typically encountered. The barrel design was modified with a degassing port to remove excess amount of water vapor from the molten mass. Initial studies without a degassing port demonstrated the presence of bubbles as well as unequal distribution of drug in the film samples.

Standard screw configuration (Figure 2-1) with three mixing zones was utilized for this study. It provided enough shear for dispersive and distributive mixing of the drug and helped get excellent content uniformity in all the extruded film formulations.

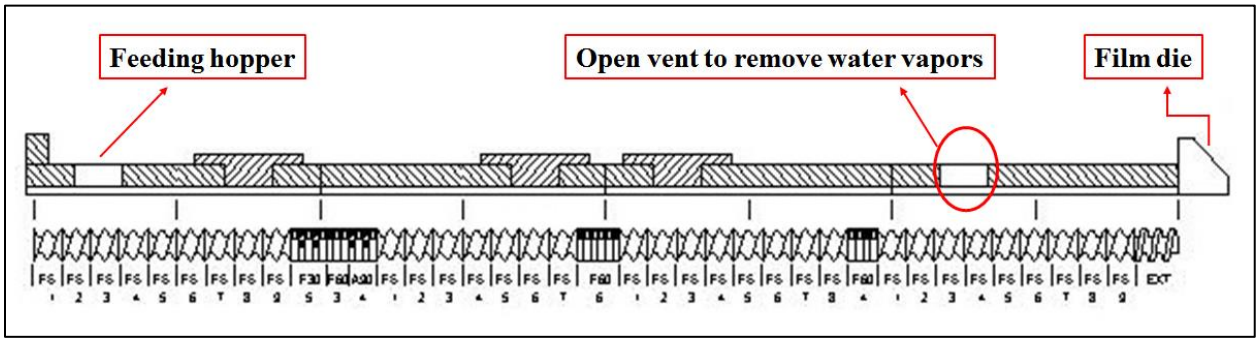



**Figure 2-1.** Film extrusion screw design

The extruded films were stretched using the roll connected to the extruder assembly. This aided in making thin films with uniform thickness, and the roll speed was optimized for steady collection of the film. The combination of processing and formulation parameters helped to manufacture uniform, clear, and very thin films (60–110 μm) using melt extruder.

## 3.2. Physiochemical evaluation of films

TGA is very critical before performing HME because the drug and excipients are exposed to high temperature during the extrusion process, and there are possibilities of drug degradation or thermally-induced chemical reactions or both (Morott et al., 2015). The TGA results (Figure 2-2) specified that API, polymer, and excipients were chemically stable in the HME processing temperature range. Lycoat® RS 780 demonstrated a loss of weight (<3%), which was attributed to the moisture present in the polymer. These results confirmed that all materials had excellent thermal stability and fit for the melt extrusion process (M. B. Pimparade, 2013).

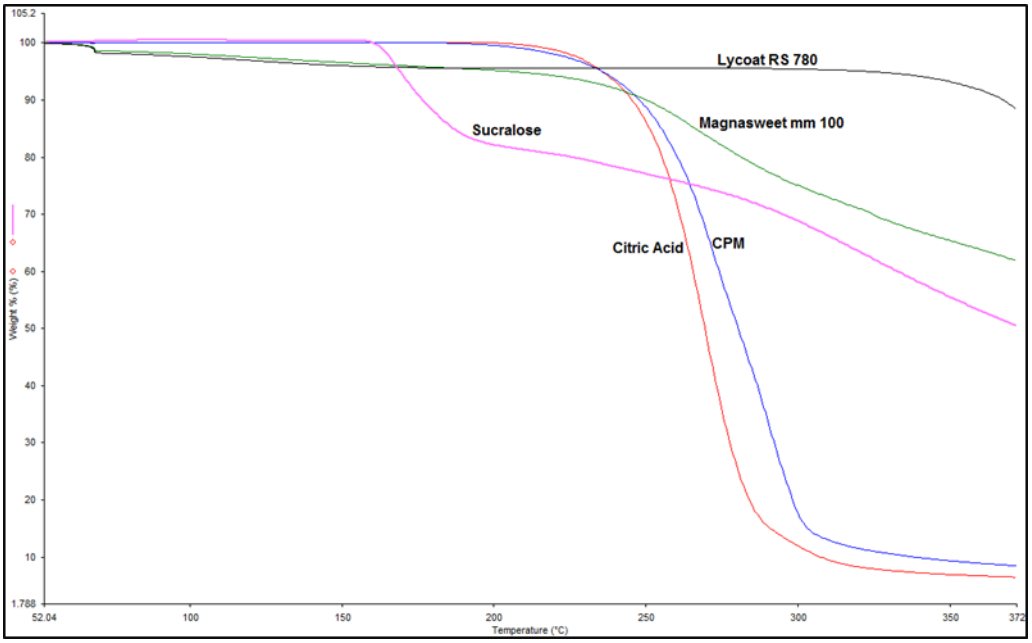



**Figure 2-2.** TGA thermograms of chlorpheniramine maleate, polymer, and excipients

XRD was used to investigate the physical state of the drug after HME process. The XRD results (Figure 2-3a & 2-3b) of CPM illustrated prominent peaks at 2θ angles of approximately 13, 19, and 20 degrees, while citric acid showed peaks at 2θ angles of 18, 19, and 26. The melt-extruded formulation did not show any peak that confirmed the presence of drug in an amorphous form. The reasons behind the complete conversion of drug to an amorphous form were the high shear during extrusion, low drug load, and relatively high amounts of glycerin. The presence of CPM and excipients in an amorphous form aided the flexibility and clear appearance of the film.

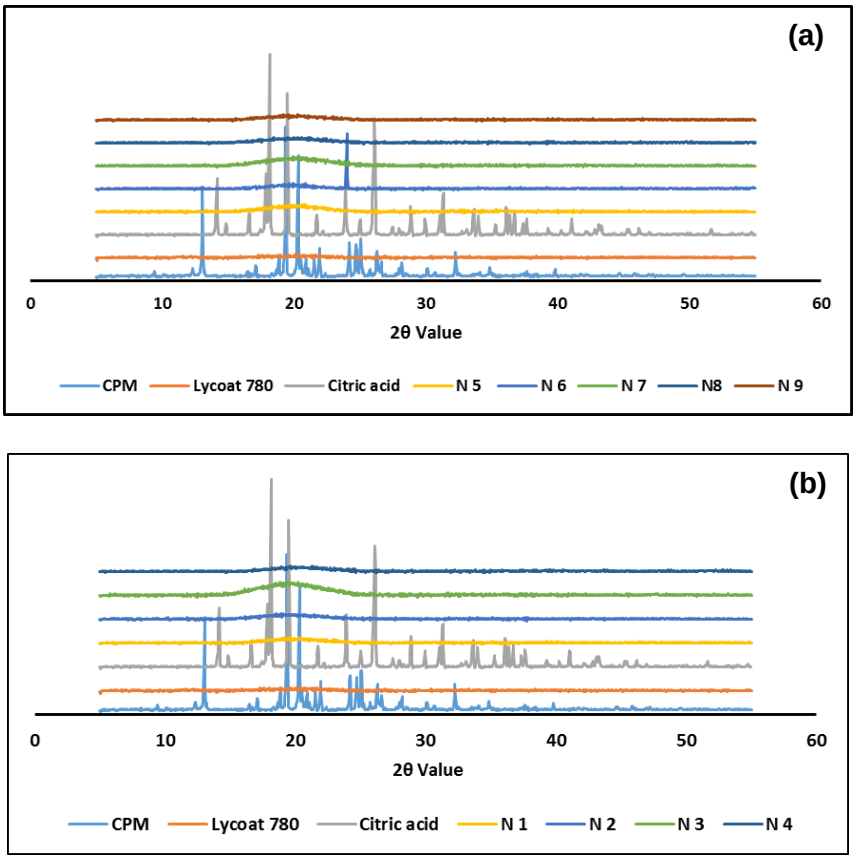


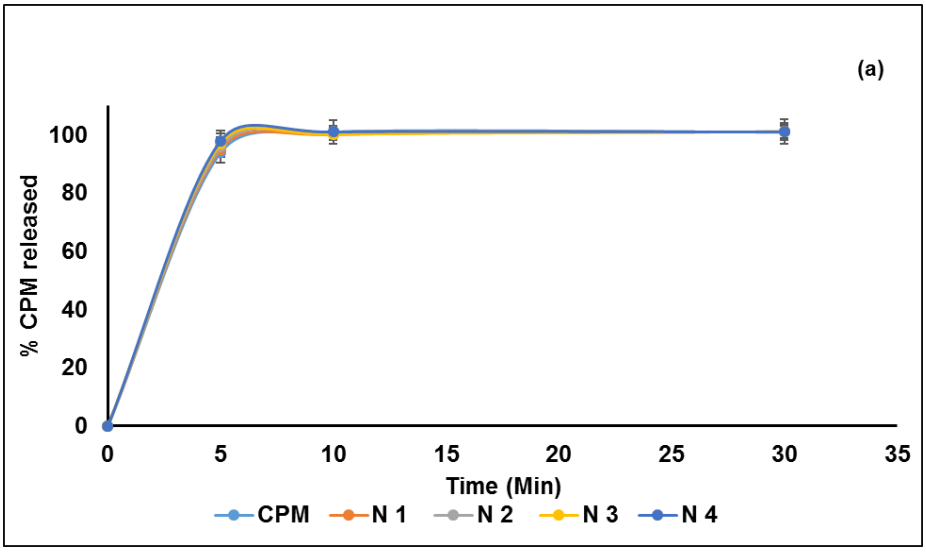

**Figure 2-3 (a) (b).** X-ray diffraction profiles of CPM, polymer, and melt-extruded film formulations

3.3. Dissolution studies

Lycoat® RS 780 is a comparatively new modified starch-based polymer, which demonstrated its significance in film coating for tablets and oral film development using solvent casting method (El-Setouhy and El-Malak, 2010; Parissaux et al., 2007). Being a non-gelling and highly water-soluble polymer, it provides rapid disintegration and dissolution to formulations. Visual inspection during dissolution demonstrated rapid disintegration of the film when it touched the dissolution media. This characteristic helps in the rapid onset of action of the formulation, because the drug can diffuse from the oral mucosa and reach the systemic circulation (Garsuch

and Breitkreutz, 2009).

During dissolution studies, the formulations rapidly release CPM, and it was attributed to hydrophilic excipients and Biopharmaceutics Classification System (BCS) class I drug. These films had very low thickness (60–110 µm) and higher surface area, which enabled interaction with dissolution media and rapid disintegration following complete dissolution. Dissolution results (Figure 2-4a & 2-4b) showed ~95% drug release in the first 5 min of the dissolution experiment, and at 10-min time points, there was complete release of the drug.



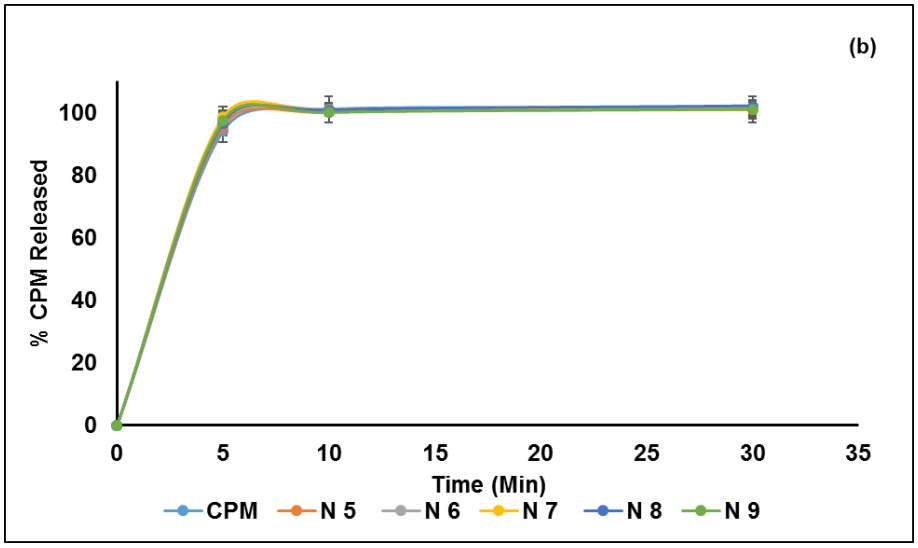



**Figure 2-4 (a) (b).** Dissolution release profiles of CPM and melt-extruded film formulations

3.4. SEM evaluation

The surface morphology was examined by SEM for all film formulations. SEM images did not exhibit CPM crystals, indicating an amorphous nature of drug in formulations (Figure 2-5). The formulations showed very smooth surface at low magnification. This affirmed the smooth texture of film surface, which is one of the esthetic attributes of films. However, at microscopic level, there was high surface area, which helped in the rapid disintegration of the film.

3.5. Film characterizations

As illustrated in Table 2-2, the film formulations demonstrated excellent D.T of 6–11 s, which was attributed to the thickness of the film and presence of water-soluble materials in the film. The formulations contained water-soluble excipients and APIs such as CPM, citric acid, glycerin, and modified starch. The most crucial parameter for disintegration is the low thickness of the film. As the films had a thickness range of 60–110 µm, they aided in the faster disintegration

of all film formulations. In addition to the low thickness of the film, the amount of saliva in the oral cavity is very critical for rapid disintegration. The normal flow of saliva in a healthy person is 0.34 mL/min, and it can be increased by the addition of agents that simulate salivary production, including citric, malic, lactic, ascorbic, and tartaric acids (Dixit and Puthli, 2009). Citric acid is the most preferred saliva-stimulating agent, and it was estimated that citric acid could increase salivary flow approximately 5-fold in 2–6% proportion in the formulation (Dixit and Puthli, 2009). With the addition of citric acid, the pH of the films was found to be in the range of 2.9–3.4 and it could contribute in improving rate of salivary flow after administration of formulation which will aid in rapid disintegration of film product.

All the film formulations were tested for their Ts and %E (Table 2-2). Ideally, the film should have desirable mechanical properties so that it can remain intact during handling and transport. ODFs showed appropriate strength and %E. These excellent mechanical properties were attributed to the presence of glycerol, citric acid, and CPM, which reduced film stiffness via disruption of intermolecular forces of the polymer owing to the accommodation of these compounds between the strands, thereby providing elasticity to the films (Entwistle and Rowe, 1979; Stubberud et al., 1996).

**Table 2-2:** Film Evaluation

| Formulation | Strength (Mpa) | Elongation (%) | Thickness (µm) | pH | D.T (Seconds) |
|---|---|---|---|---|---|
| **N 1** | 10.03 (±1.017) | 9.93 (±0.702) | 70 (±10) | 3.13 (± 0.006) | 6 (±1) |
| **N 2** | 20.87 (±1.014) | 7.91 (±0.367) | 70 (±10) | 3.00 (± 0.050) | 7 (±1) |
| **N 3** | 5.79 (±0.487) | 14.00 (±0.958) | 70 (±15) | 2.88 (± 0.025) | 6 (±2) |
| **N 4** | 7.80 (±1.014) | 12.04 (±0.467) | 100 (±20) | 2.90 (± 0.035) | 11 (±1) |
| **N 5** | 3.55 (±0.941) | 127.12 (±10.400) | 110(±13) | 3.39 (± 0.076) | 9 (±2) |
| **N 6** | 10.82 (±0.146) | 9.88 (±0.163) | 100 (±10) | 3.37 (± 0.023) | 7 (±1) |
| **N 7** | 6.84 (± 0.440) | 9.77 (± 0.061) | 60 (±18) | 3.21 (± 0.032) | 6 (±1) |
| **N 8** | 11.04 (± 0.92 | 11.30 (± 0.390) | 110 (±21) | 3.18 (± 0.006) | 6 (±1) |
| **N 9** | 5.39 (± 0.590) | 16.34 (± 6.720) | 100 (±14) | 3.11 (± 0.006) | 7 (±1) |

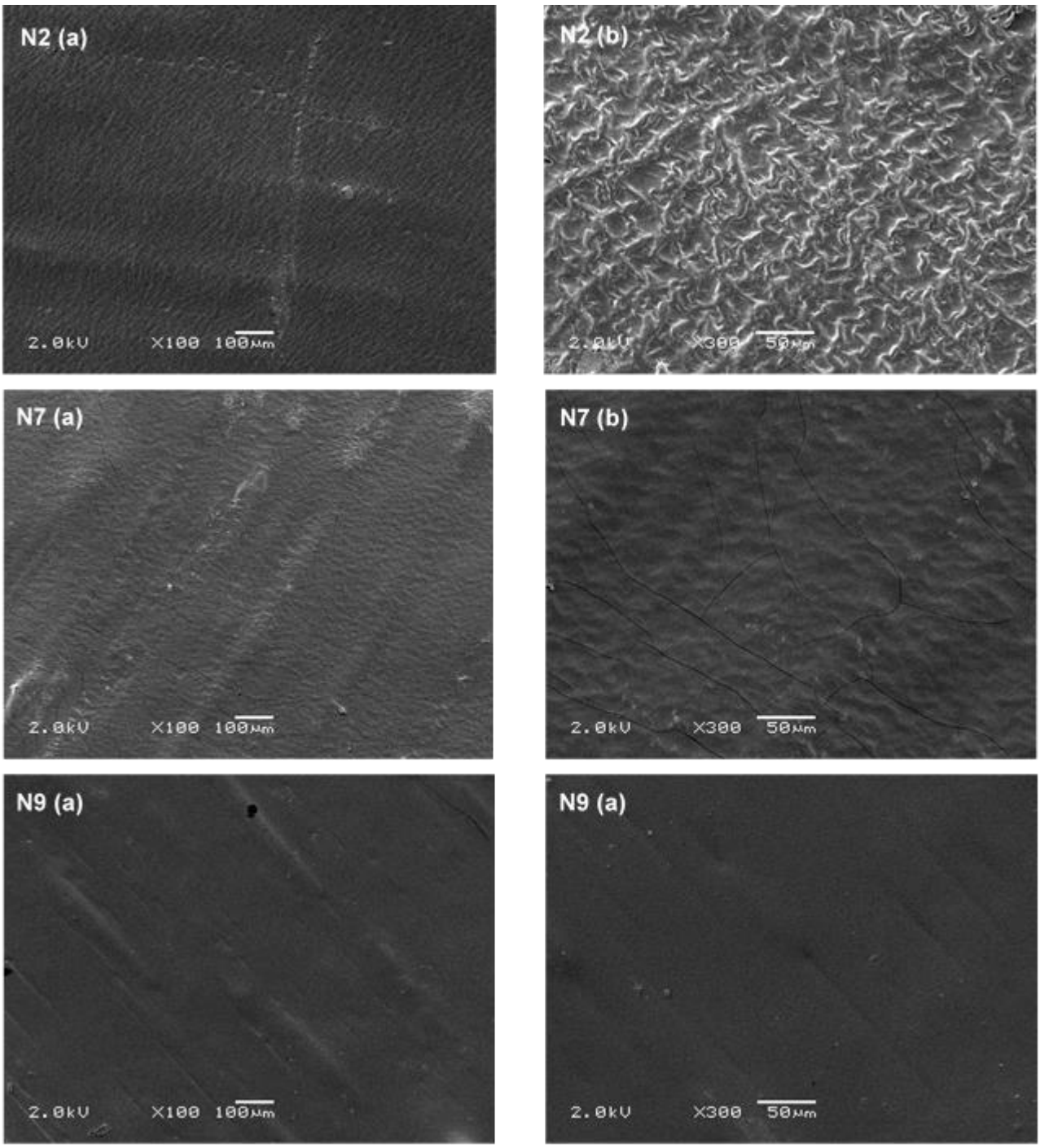



**Figure 2-5.** Scanning electron microscopy (SEM) images of films: formulation N2 (a, b), N7 (a, b), and N9 (a, b)

3.6. *In vivo* taste evolution

Firstly, the taste perception of rats was evaluated by administering 0.5 and 1 mg/mL CPM dissolved in distilled water. These results were important to avoid taste variability between animals (Figure 2-6), and showed that the rats consumed ~10 and ~14 mL of water in 15 and 30 min, respectively. The results of this study were comparable with those of the study published by Tiwari et.al. Thus, the rate and extent of consumption of water were reduced significantly to ~3 and ~5 mL in 15 and 30 min with the administration of 0.5 mg/mL CPM solution. At a higher concentration of 1 mg/mL, there was notable reduction in consumption of water to ~1.6 and ~2 mL at 15 and 30 min. Notably, this reduction in consumption of CPM solution despite deprivation of water for 22 h affirmed an aversion toward CPM. Moreover, aversion behaviors (Figure 2-7), such as jaw smacking, oral grooming, nose wrinkle, paw wipe, forelimb flail, head shake, paw shakes, and retreating confirmed the dislike of rats toward the drug solution (Tiwari et al., 2015).

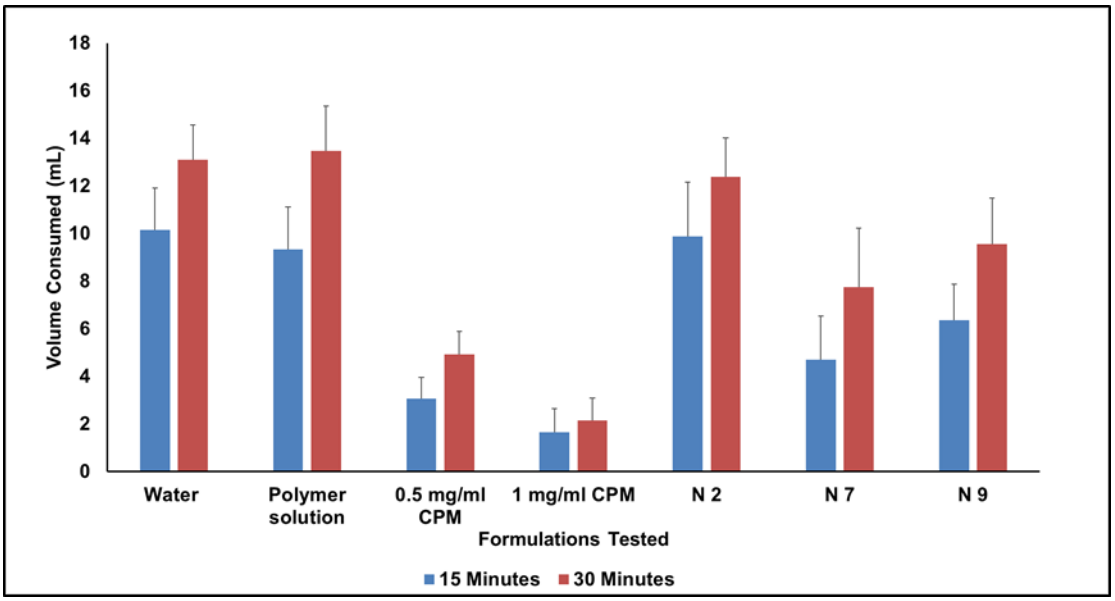



**Figure 2-6.** Taste evaluation in rat model

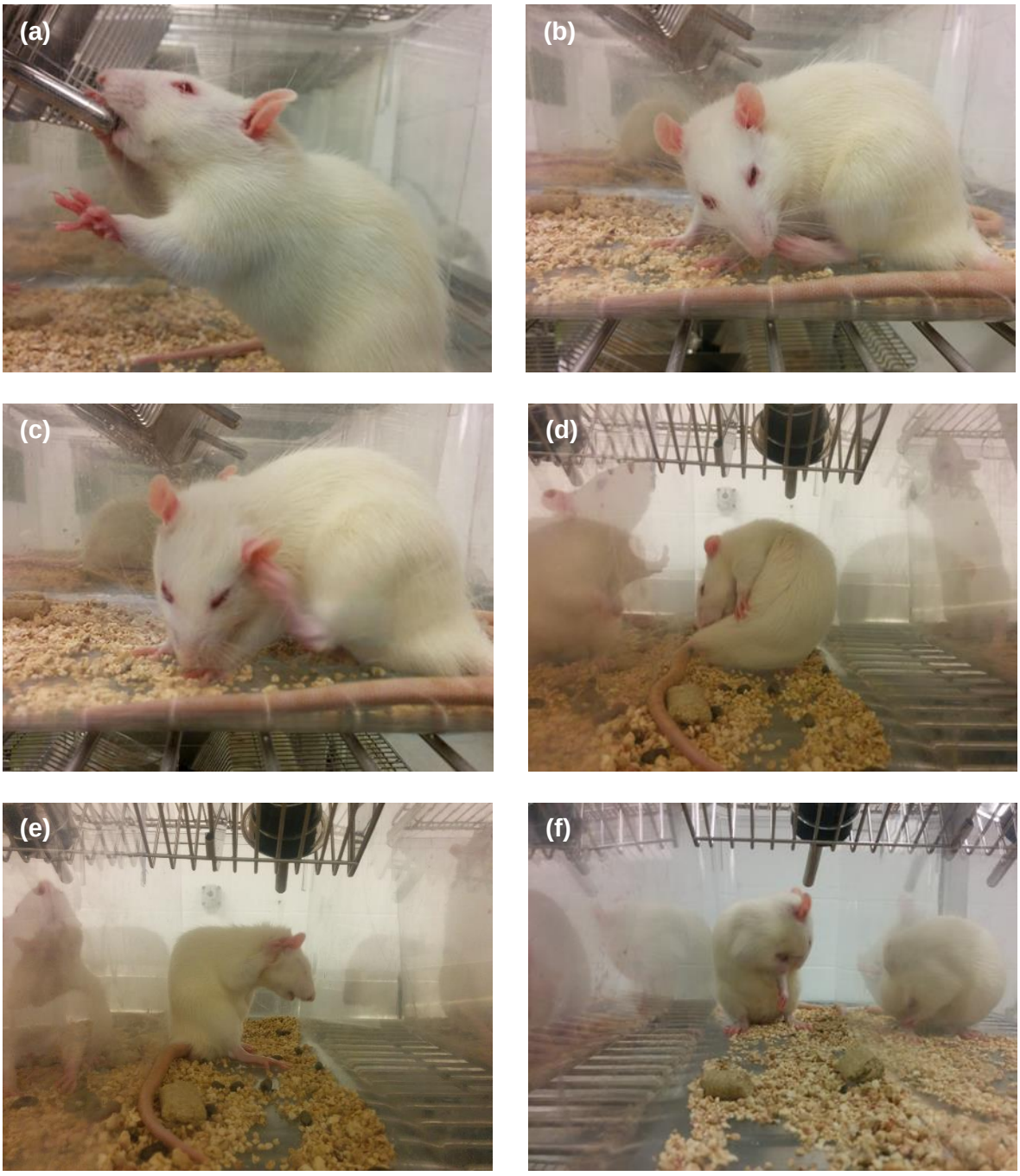



**Figure 2-7.** Behavioral response of rats after administration of CPM and formulation solutions, a) Normal Drinking b) Paw licking c) Scratching by paw d) Biting e) Scratching by both paws f) Oral grooming

As illustrated in Figure 2-6, the rats consumed ~10 and 12.5 mL of N 2 solution (5% CPM in the film) in the first 15 and 30 min, and the amount was comparable with the consumption of water. In addition, N7 (10% CPM) exhibited consumption of ~ 4.7 and ~8 mL at 15 and 30 min. Furthermore, N9 (7.5% CPM) showed consumption of ~6.3 and 10 mL at 15- and 30-min time point. These results indicated that with increasing concentrations of CPM, there was noticeable reduction in the consumption of formulation. The rats did not show aversion behavior such as forelimb flail with N2 formulation. However, there was a surge in the aversion behavior response upon increasing the drug concentrations in N7 and N9.

The results of this study were very helpful to understand about the taste of pure drug and formulation. It provided an insight into the taste of products, which helped to screen this formulation for human studies.

### 3.7. Film evaluation by human panel

Before evaluation of taste of the formulation, it is very important to understand the taste perception of human volunteers to minimize intra-subject variability. Taste perception study was performed on six healthy human volunteers. Initially, different concentrations of CPM in 2 mL of water were administered to the human subjects. Three subjects had threshold at 0.5 mg and the remaining three subjects reported moderate bitterness at the same concentration. A dose of 2.5 mg demonstrated bitterness in all subjects, and only three volunteers could taste higher concentration of CPM (4 mg, Table 2-3). This initial evaluation confirmed the appropriateness of the subjects for taste masking study.

**Table 2-3:** Human taste perception response

| Amount of CPM/2ml | Volunteer 1 | Volunteer 2 | Volunteer 3 | Volunteer 4 | Volunteer 5 | Volunteer 6 |
|---|---|---|---|---|---|---|
| **0** | | | | | | |
| **0.5** | 1 | 1 | 3 | 3 | 3 | 1 |
| **1** | 3 | 2 | 4 | 5 | 4 | 2 |
| **2.5** | 4 | 3 | 5 | | 5 | 3 |
| **4** | 5 | 5 | | | | 5 |

The results of taste masking evaluation in animal model suggested that formulation N2 with 5% CPM had significant taste masking. Moreover, this formulation had an excellent D.T (7 s) in *in vitro* studies. Based on these results, N2 formulation (4 mg CPM in each film) was considered for human panel taste and disintegration studies to ascertain the product attributes in human subjects. The physical mixture of N2 exhibited disagreeable and unendurable taste in human volunteers (an average score of 5 on a scale of 1-5; Figure 2-8). These findings asserted that the administration of CPM with modified starch and other excipients (physical mixture) did not assist in diminishing the bitterness of the drug, and it required a pertinent formulation approach. When the film formulation was administered, there was notable reduction in bitterness to ~3 on the scale of 1-5. Statistical analysis of the human panel data suggested a significant difference in bitterness ($p<0.0001$) between the physical mixture and melt-extruded ODF samples.

The volunteers were asked to report the time for complete disintegration of films in the oral cavity, and the average D.T was 16±4.5 s for N2 formulation. The rapid D.T was attributed to the thickness of film (~70 µm) and the use of hydrophilic polymer in the formulation. Notably, the

thickness of N2 formulation was comparable with commercially available mouth-refreshing films (~60 µm) (Dave et al., 2014). Furthermore, human subjects did not report any stickiness or difficulties in handling and no particulate matter after disintegration of films. Currently, there are no regulatory guidelines available for the thickness, D.T, and other quality attributes of the film; however, there are guidelines for ODT suggesting a D.T of 30 s. We are considering 30 s as a reference D.T for the film product.

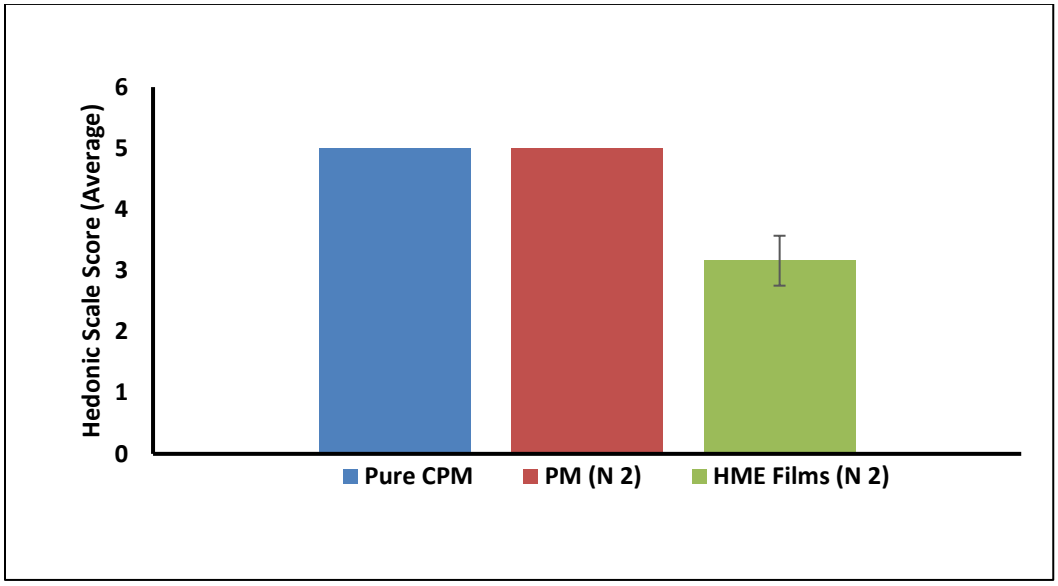



**Figure 2-8.** Human taste panel evaluations: pure CPM, physical mixture (N2), and melt-extruded film (N2)

## 4. Conclusion

This innovative study demonstrated the utilization of HME technology for continuous manufacturing of orally disintegrating films. A standard screw configuration with a degassing port was used to manufacture thin, bubble-free, uniform, and esthetic film formulations. The films showed immediate disintegration and dissolution, which were attributed to the thinness and presence of hydrophilic excipients in the formulations. The rat model exhibited excellent bitterness discrimination in different drug-loaded formulations. Human panel study confirmed the reduction of bitterness in the films compared to the pure drug and physical mixture. Moreover, the disintegration results were in accordance with those of the *in vitro* method. This formulation could be used as a platform for the development of solvent-free thin film formulations focusing on pediatric and geriatric patients.

# CHAPTER III

## Double Extrusion as a Novel Approach for Product Development


## Abstract

The novel double extrusion approach was utilized for the development of fixed dose combination. For this study, carbamazepine and caffeine citrate were selected as model drugs, and hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC) and polyethylene oxide (PEO) were as polymeric carriers. Standard screw design was used for first extrusion and modified screw design for second extrusion. Two step dissolution was performed on extrudated formulations which demonstrated significantly different release profile compared to single extrudated formulations. The solid-state characterizations confirmed the presence of drug in an amorphous form and could not find any chemical interaction. In addition, the FTIR-chemical imaging results showed the uniform distribution of drugs in double extrudated formulations.

# 1. Introduction

Hot Melt Extrusion (HME) is a process of pumping material under high shear and at an elevated temperature (Pimparade et al., 2015). It reduced the use of solvent in formulation process and helped to make manufacturing process continuous. Melt extrusion demonstrated its utility in the development of solid oral dosages form which included immediate release, controlled release, taste masked, films and abuse-deterrent formulations (Pimparade et al., 2015; Repka et al., 2007; Repka and McGinity, 2001; Sarode et al., 2013; Zhang and McGinity, 1999). It exhibited unique advantages of being solvent free, continuous, single-step process, easy to scale up and low floor area (Repka et al., 2007). HME is a versatile technique and could be modify as per the need.

In recent years, Co-extrusion technology demonstrated its utility for the development of pharmaceutical dosages forms and medical devices (Vynckier et al., 2014). It proved its significance in plastic, food and metal industry for developing everyday products (Vynckier et al., 2014). It is a simultaneous extrusion of two or more material creating a multi layered extrudates (Dierickx et al., 2012). Co-extrusion exhibited some of the distinctive advantages like implants and fixed dose combinations, with a potential for the development of some of the complex formulations (Fischer, 2008; Vynckier et al., 2014). Despite its advantages, co-extrusion is an expensive processing technique due to the use of two extruder assemblies and large amount of space required for the instrument (Vynckier et al., 2014). Additionally, it is not feasible to use this process during early phase of product development as there is an inadequate supply of APIs.

While keeping the advantages of co-extrusion process, we propose a novel double extrusion process which involve two-time extrusion with two polymers at a different glass transition temperature (Figure 3-1). In this process, the first extrusion is performed with high Tg

polymer and a drug, and the second extrusion with a significantly low Tg polymer with the same or a different drug. This novel approach could contribute in the development of fixed dose combination or taste masked formulation. This process is economical and could help to modify release characteristics by process modification without altering formulation compositions.

The main objective of this study was to evaluate the feasibility of double extrusion approach for the development of solid oral formulations. Carbamazepine and caffeine citrate were selected as model drug based on their solubility and high molecular weight hydroxypropyl methylcellulose (HPMC) and low molecular hydroxypropyl cellulose (HPC) with Polyethylene oxide (PEO) were used as a polymer matrix. As per the literature available, this is the first attempt to utilize double extrusion approach for the development of solid oral dosages form.

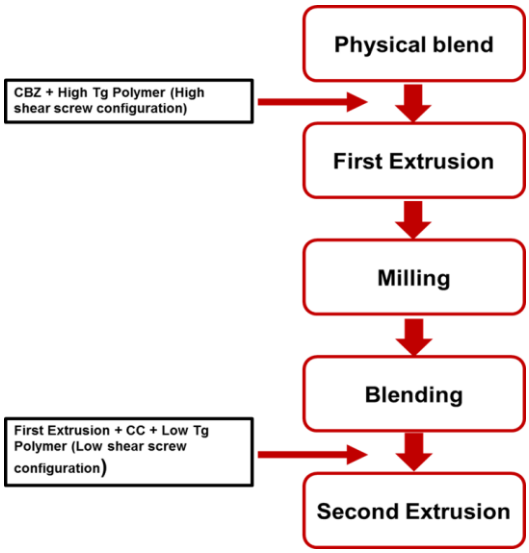



**Figure 3-1.** Schematic representation of double extrusion technique

## 2. Materials and Method

### 2.1. Material

Carbamazepine (CBZ) was purchased from Afine Chemicals Limited (Zhejiang, China). Caffeine citrate (CC) and stearic acid were ordered from Fisher Scientific (Pittsburgh PA, USA). Benecel™ K15M (HPMC) and Klucel™ HPC ELF was supplied by Ashland Specialty Ingredients (Wilmington, DE, USA). Coloron (West point, PA, USA) were kind enough to contribute Polyox™ N10 (PEO-N10) for the study.

### 2.2. Thermogravimetric Analysis (TGA)

Thermogravimetric analysis studies (Perkin Elmer Pyris 1, Shelton, CT, USA) were performed to estimate the thermal stability of the APIs and excipients during HME processing. The data was analyzed using Pyris software. The API excipients were heated from 30 – 180°C at 20°C/min.

### 2.3. Preparation of Melt Extrudate Formulations

Carbamazepine (CBZ) was blended with HPMC and stearic acid was in an amount outlined in Table 3-1 using a V-shell blender (GlobePharma, Maxiblend, New Brunswick, NJ, USA) after passing through ASTM #30 mesh. The blends were melt-extruded using a co-rotating twin-screw extruder (11 mm, Process 11, ThermoFisher Scientific, Pittsburgh, PA, USA) with a standard screw design at 50 rpm over a temperature range of 160–165°C. Extrudates (Core) were milled using a comminuting mill (Fitzpatrick, Model “L1A”) and sieved through an ASTM # 35 mesh screen. The milled extrudates (Core) were mixed with Klucel™ HPC ELF, PEO N10 or

combination of both these polymers and caffeine citrate (CC) and double extruded (DE) with a modified screw design over a temperature range of 70–75°C (Table 3-2). Also, to do a comparison between the formulation prepared by double extrusion (DE) and single extrusion (SE) processes, a formulation was prepared using SE with all the contents in the same proportion as used in the DE formulation and melt extrudated at 50 rpm over a temperature range 160–165°C. Both the final formulations were pelletized to a 1 mm size.

**Table 3-1:** Single extrusion formulations

| Formulations (% w/w) | CBZ | CC | Benecel™ K15M HPMC K15 | STEARIC ACID | PEO | Klucel™ HPC ELF | Klucel™ HPC ELF: PEO (1:1) |
|---|---|---|---|---|---|---|---|
| Core | 20 | -- | 70 | 10 | -- | -- | -- |
| SE1 | 10.63 | 4.25 | 37.23 | 5.31 | 42.55 | -- | -- |
| SE2 | 10.63 | 4.25 | 37.23 | 5.31 | -- | -- | 42.55 |
| SE3 | 10.63 | 4.25 | 37.23 | 5.31 | -- | 42.55 | -- |

**Table 3-2:** Double extrusion formulations

| Formulations (% w/w) | Core | CC | PEO | Klucel™ HPC ELF | Klucel™ HPC ELF:PEO (1:1) |
|---|---|---|---|---|---|
| DE1 | 53.19 | 4.25 | 42.55 | -- | -- |
| DE2 | 53.19 | 4.25 | -- | -- | 42.55 |
| DE3 | 53.19 | 4.25 | -- | 42.55 | -- |

## 2.4. Differential Scanning Calorimetry (DSC)

DSC studies were performed with a Perkin Elmer Diamond differential scanning calorimeter (DSC) equipped with Pyris software (Shelton, CT, USA). Samples were prepared by sealing 3-5 mg of pure APIs, polymers and milled extrudates in hermetically sealed aluminum pans and heated from the temperature range of 30°C to 220°C at the heating rate of 20°C/min under an inert nitrogen atmosphere at a flow rate of 20 mL/min.

## 2.5. Fourier Transforms Infrared Spectroscopy (FTIR) with Chemical Imaging

Infrared spectra were collected using a bench top Fourier Transform Infrared (FTIR) Spectrometer (Agilent Technologies, Cary 660; Agilent, Santa Clara, CA, USA) fitted with a MIRacle ATR sampling accessory (Pike Technologies, Madison, WI, USA). The bench top ATR was equipped with a single bounce diamond-coated ZnSe internal reflection element. Chemical images were collected using an infrared microscope (Agilent Technologies, Cary 620 IR; Agilent, Santa Clara, CA, USA) equipped with a 64 x 64 focal plane array detector. The images were collected with a germanium micro ATR sampling accessory, providing a field of view (FOV) of approximately 70 x 70 µm with 1.1 µm spatial resolution.

## 2.6. Analytical Method

A Waters High performance liquid chromatography (HPLC) system equipped with a Waters 600 binary pump, Waters 2489 UV/detector, and Waters 717 plus autosampler (Waters Technologies Corporation, 34 Maple St., Milford, MA 0157) and a Phenomenex Luna 5um C18 (2) 250 x 4.6 mm column (Torrance, CA, USA) were used at a detection wavelength of 273 nm for caffeine citrate and 285 nm for carbamazepine. The mobile phase for caffeine citrate and

carbamazepine consisted of Methanol and water at a ratio of 70:30 (v/v). The mobile phase flow rate was maintained at 1.0mL/min. and an injection volume of was 20 μL was used. HPLC data was analyzed using Empower V. Software (Milford, MA, USA).

### 2.7. *In vitro* Dissolution Studies

*In vitro* drug release was measured using USP dissolution apparatus I ((Hanson SR8, Chatsworth, CA) set at 100 rpm. The test dissolution media were 700 ml of 0.1N HCl (pH 1.2) for the first 2 h, then 200 ml of 0.2 M tribasic sodium phosphate (pH 12.5) to provide a final pH of 6.8 (dissolution media temperature maintained at 37 ± 0.5°C). Dissolution samples were withdrawn and analyzed by HPLC-UV system.

### 2.8. Scanning Electron Microscope (SEM)

The surface morphology of pellets was evaluated using Scanning electron microscopy (SEM) analysis. Samples were mounted on adhesive carbon pads placed on aluminium and were sputter coated with gold using a Hummer sputtering system (Anatech Ltd, Springfield, VA, USA) in a high vacuum evaporator. A JEOL JSM-5600 scanning electron microscope operating (SEM) at an accelerating voltage of 10 kV was used for imaging.

# 3. Result and discussion

## 3.1. Thermal stability

Thermogravimetric analysis confirmed that the APIs and excipients did not show any degradation in the extrusion processing temperature. Only cellulosic polymer, HPC and HPMC demonstrated < 3 % loss which was attributed to the presence of surface moisture in these polymers (Figure 3-2). This result affirmed the thermal stability of these APIs and the excipients for melt extrusion process.

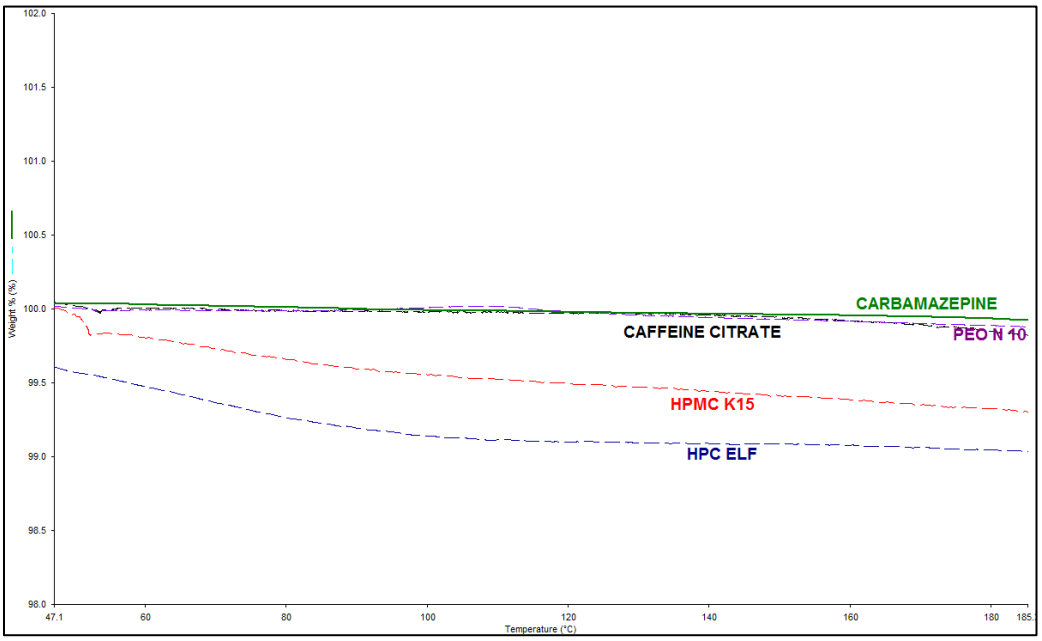



**Figure 3-2.** TGA thermograms of carbamazepine and, polymer.

## 3.2. Preparation of Melt Extrudated Formulations

Initially, pure HPMC was used to extrude with CBZ but it generated very high torque and consequently, halted the extruder completely. It happened due to the high glass transition HPMC. Thus, it raised a need for suitable plasticizer which reduces the glass transition temperature and

improves processability during extrusion process. Steric acid was used as a plasticizer in all the formulations.

For the extrusion of core formulation, a standard screw configuration (Figure 3-3a) was utilized which consisted of three kneading zone. It helped to get dispersive and distributive mixing and consequently, contributed to convert crystalline carbamazepine into an amorphous form. Carbamazepine is classified as a BCS II and its solubility is a rate limiting parameter for release, however, extrudated formulation with CBZ demonstrated improved dissolution rate as compared to neat API and it was attributed to the extrusion processing conditions.

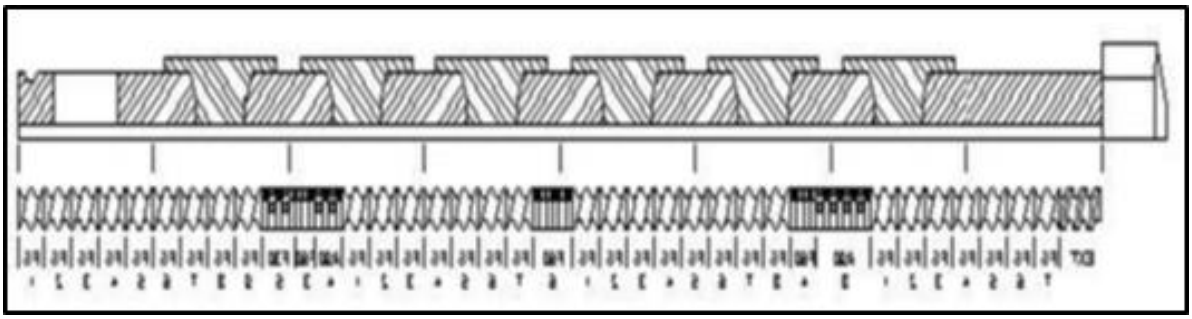


**Figure 3-3a.** First extrusion screw design

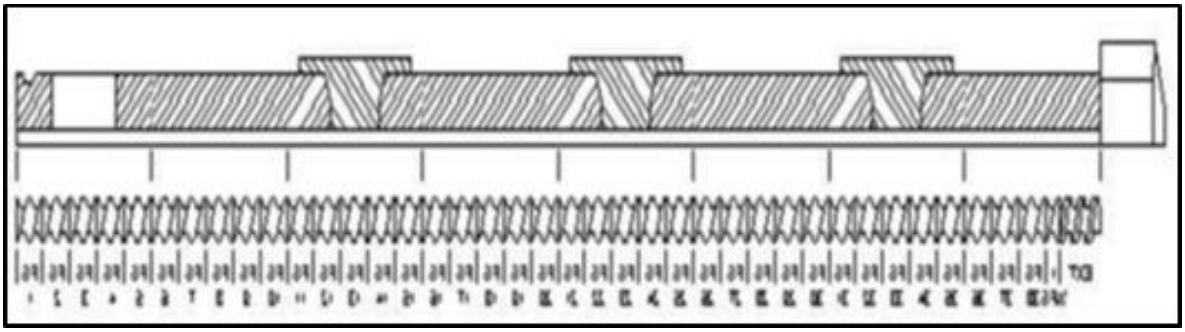


**Figure 3-3b.** Double extrusion screw desig**n**

Second extrusion was performed with modified screw configuration (Figure 3-3b) with no kneading elements to minimize the shear and avoid the intermixing of first extrudate (core) formulation. Also, extrusion temperature was well below the glass transition temperature of HPMC which helped to keep CBZ in relevant polymeric matrix. The milled first extrudates was mixed with caffeine citrate and low molecular weight polymers, and extrudated at 70-75°C.

To compare the double extrudated formulation, all the components were mixed together and extrudated with the standard screw configuration with same processing condition like core formulations.

## 3.3 Differential Scanning Calorimetry

DSC thermogram showed a characteristic endothermic peak for pure Carbamazepine, caffeine citrate, stearic acid and polyethylene oxide, which proved the crystalline nature of APIs and excipients.

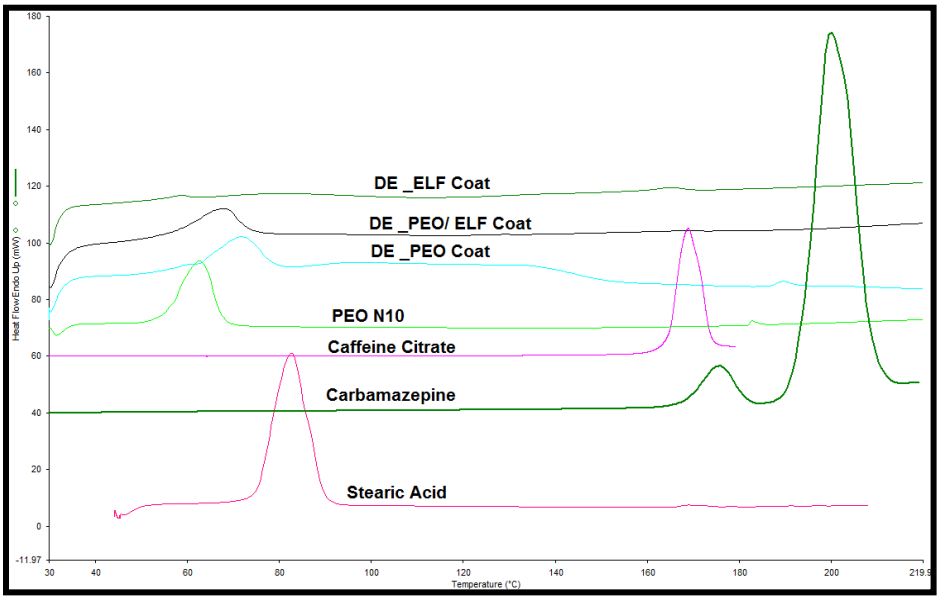



**Figure 3-4a.** DSC Thermogram of DE formulations

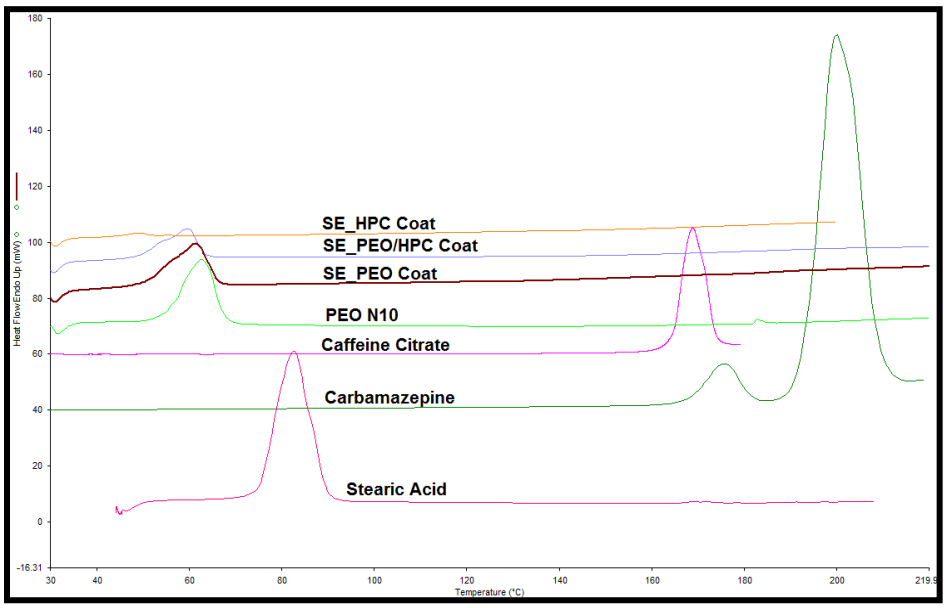



**Figure 3-4b.** DSC Thermogram of SE formulations

Double extrudated formulations DE1, DE2 and DE3 (Figure 3-4a) did not exhibit any endothermic peak which confirmed the complete conversion of CBZ and CC in an amorphous form. It was attributed to the screw design utilized for the extrusion which imparted high shear and aided in conversion of crystalline CBZ to amorphous form. Also, caffeine citrate did not demonstrate a crystalline peak and it was attributed to the solublization of drug in polymeric matrix.

Single extrudated SE1, SE2 and SE3 (Figure 3-4b) formulations did not exhibit melting peak and these results were comparable with DE formulations. The selection of high shear standard configuration was the key factor for physical transformation of drug in an amorphous form.

## 3.4. Investigation of Extrudates Uniformity

FTIR Chemical Imaging was utilized to evaluate the distribution of CBZ and CC in double

extrudated formulations at microscale level. Multiple positions of extrudates were investigated using Attenuated Total Reflectance (ATR) that directly touched the sample surface. The wavenumber of 1597 $cm^{-1}$ and 1763 $cm^{-1}$ which are unique to carbamazepine and caffeine citrate in formulation were utilized to produce chemical images of formulations (Figure 3-5a). Figure 3-5b and Figure 3-5c are representative of the infrared images taken with a Micro ATR at a 1.1 µm spatial resolution and 70 x 70 µm FOV. In all the collected images APIs were uniformly distributed in extrudates. The small area with elevated CBZ and CC concentration which were represented by red or orange color are evenly distributed in the extrudates. The homogenous distribution of APIs in pellets suggested invariable release in each extrudated pellets. Moreover, these results affirmed the appropriateness of screw configurations for first and second extrusion.

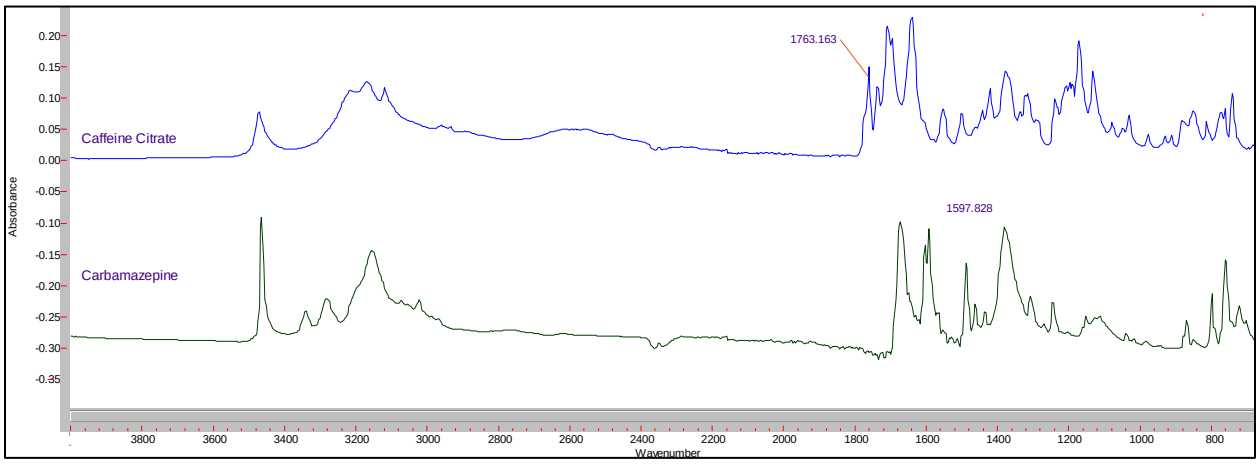



**Figure 3-5a.** FTIR spectra of carbamazepine and caffeine citrate

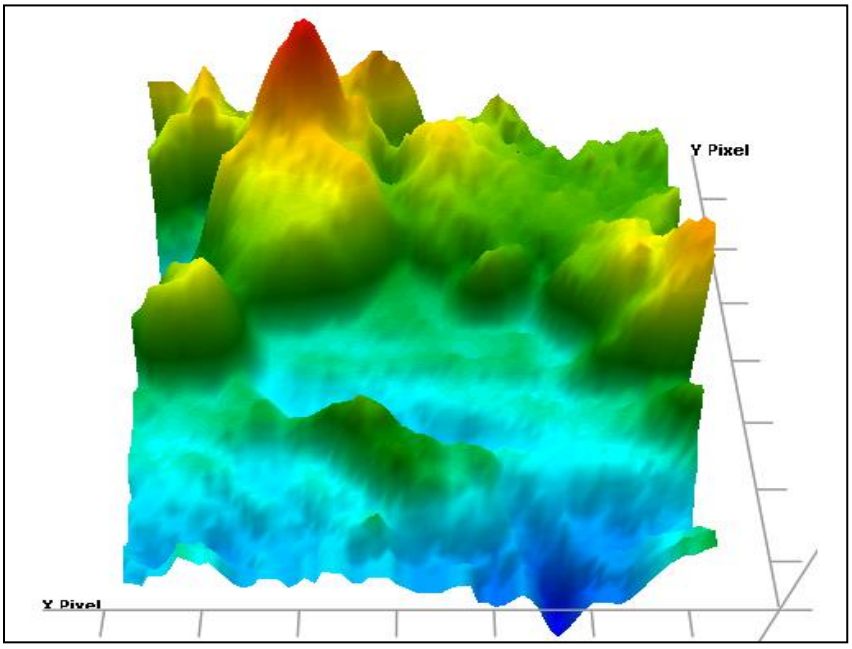



**Figure 3-5b.** FTIR chemical image of DE2 – CBZ

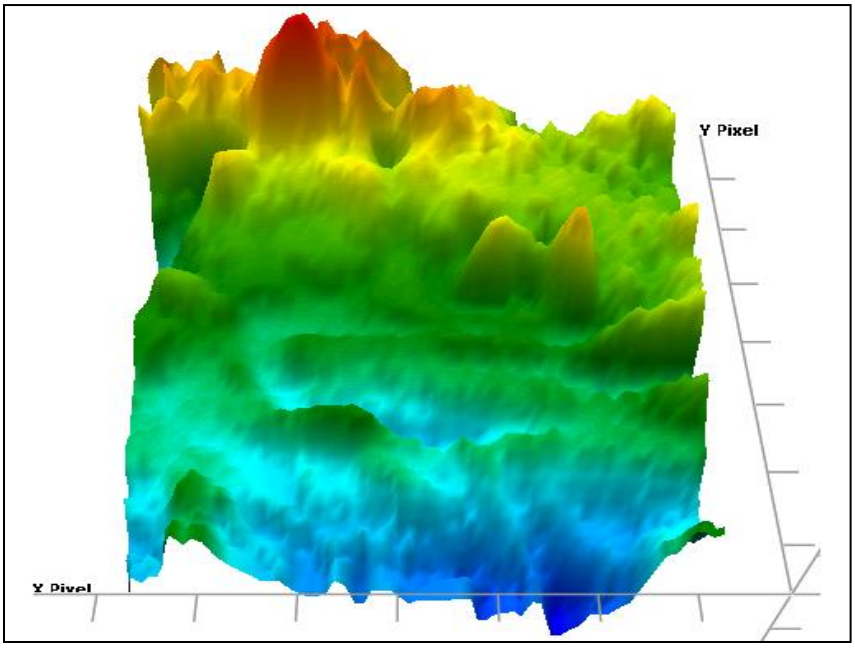



**Figure 3-5c.** FTIR chemical image of DE2 – CC

3.5. *In vitro* Dissolution Studies

Two step dissolution was performed on the melt extruated formulations. Double extrudated formulation demonstrated slow and steady release of carbamazepine compared to single extrudated formulations. Formulation DE 1 with PEO N 10 as a second polymeric matrix showed comparative fast release to DE 2 (1:1 PEO N 10 and HPC ELF) and DE 3 (HPC ELF). The difference in the release profile was attributed to the selection polymeric matrix and its proportions.

The CBZ release profile for single extrudated formulations demonstrated rapid release compared to double extrudated formulations (Figure 3-6a & 3-6b). In DE formulations, core matrix remained intact during second extrusion and there was also a second polymeric coat which acted as a barrier for the release of CBZ. However, in SE, the drug was dispersed throughout the pellets and CBZ was exposed to the outer layer which contributed in quick release of CBZ compared to DE.

The caffeine citrate exhibited fast release in DE formulation and this was due to the presence of CC in outer layer with immediate releasing matrix (Figure 3-7a &3-7b). On the contrary, in SE formulations caffeine citrate was distributed in high molecular weight HPMC matrix which hindered the release and it required significantly more time for complete release of drug.

This data suggested that with the change in extrusion processing steps, there were noteworthy differences in release profile without modifying any compositions or proportions.

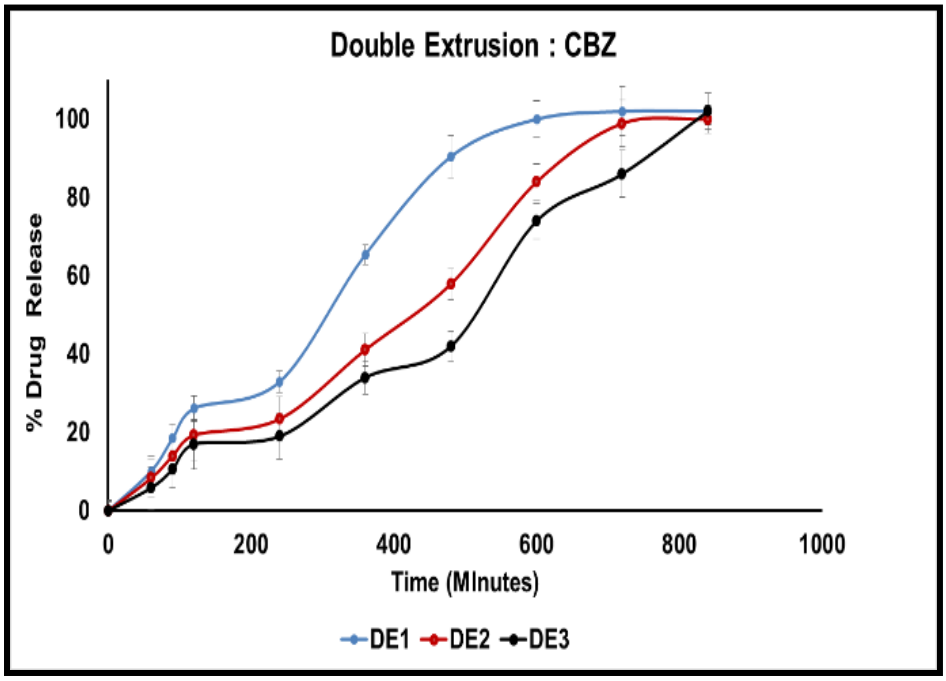



**Figure 3-6a.** Two step dissolution - DE CBZ

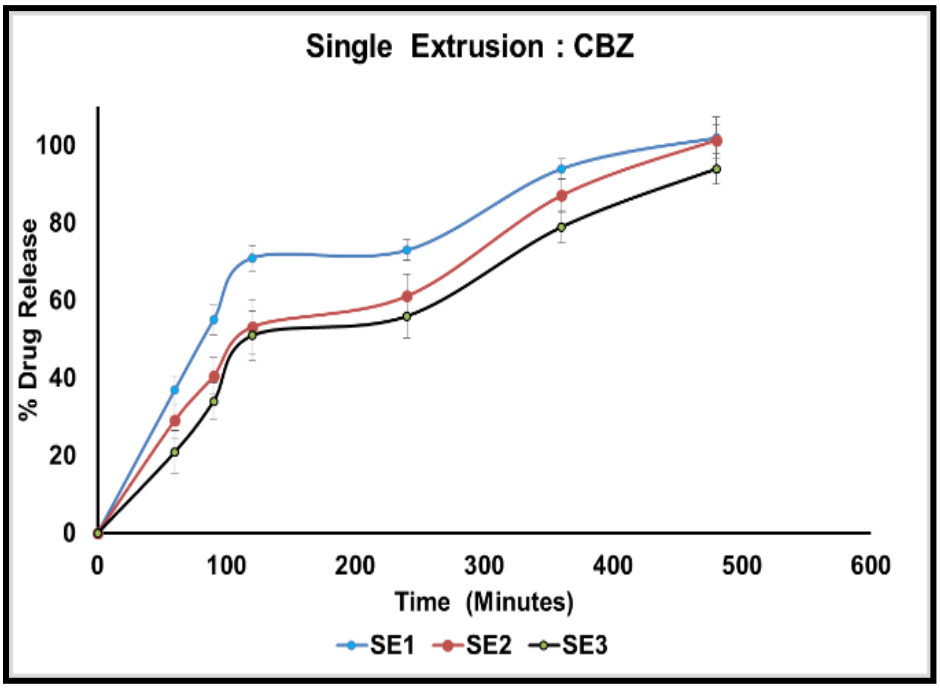



**Figure 3-6b.** Two step dissolution - SE CBZ

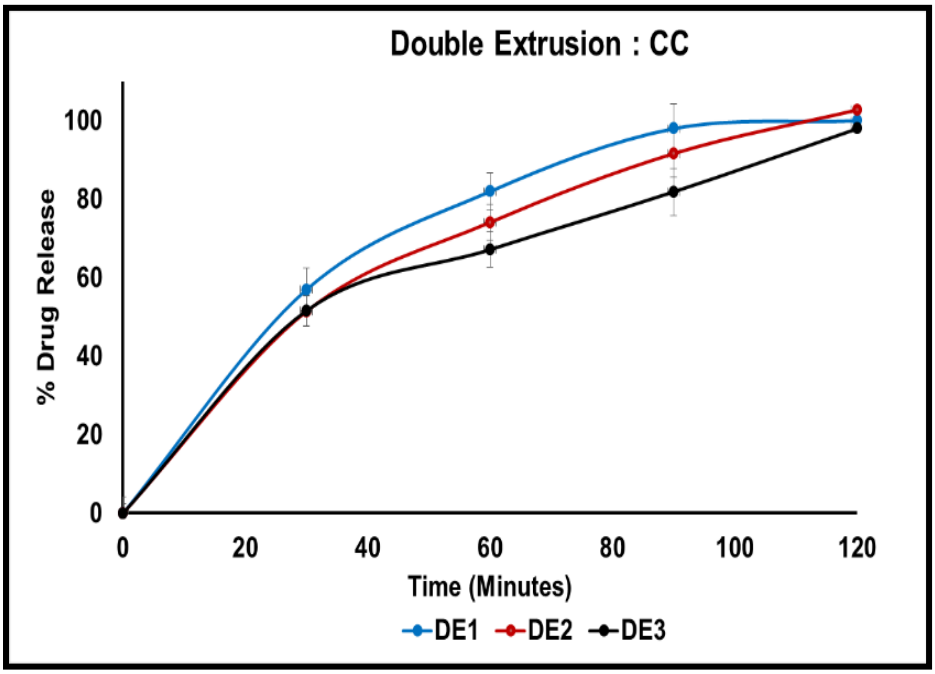



**Figure 3-7a.** Two step dissolution - DE CC

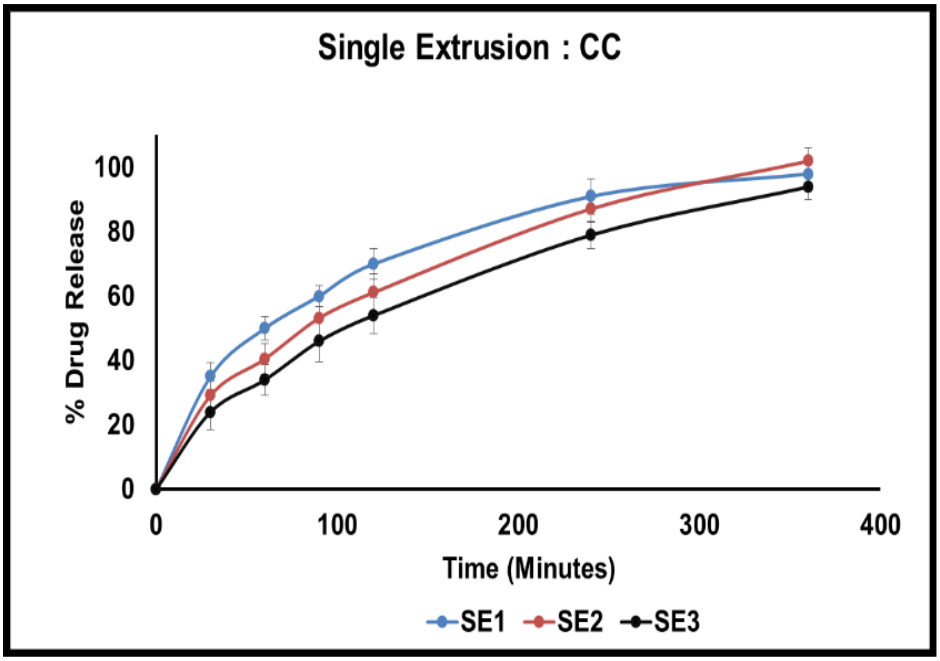



**Figure 3-7b.** Two step dissolution - SE CC

3.6. SEM Evaluations

SEM analysis of the DE and SE formulations confirmed the different physical appearance at microscopic level. Double extrudated formulation DE 2 with PEO N10 and HPC ELF as second extrudated matrix demonstrated very uniform outer layer and it was due to the presence of only low Tg polymer on outer side of extrudates. On the other hand, the formulation SE 2 with same composition as DE 2 demonstrated very different appearance at microscopic level and it was due to the presence of HPMC along with PEO and HPC ELF. These results confirmed that this double extrusion approach helped to separate the core matrix and outer polymeric matrix. Also, it provided the different release profile due to the variation in extrusion processing condition.

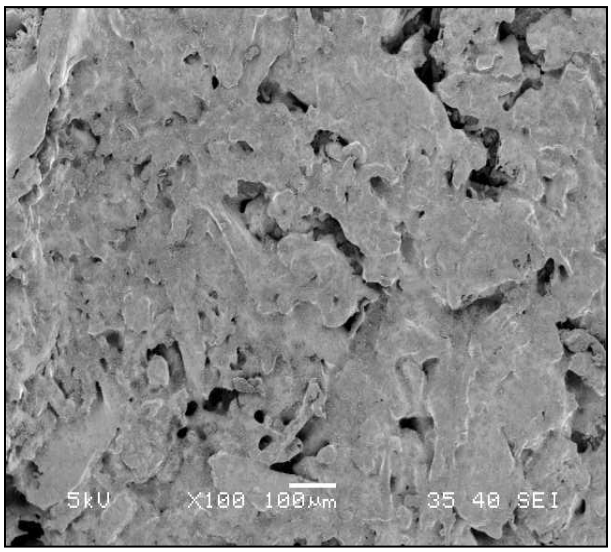



**Figure 3-8a.** SEM image DE2

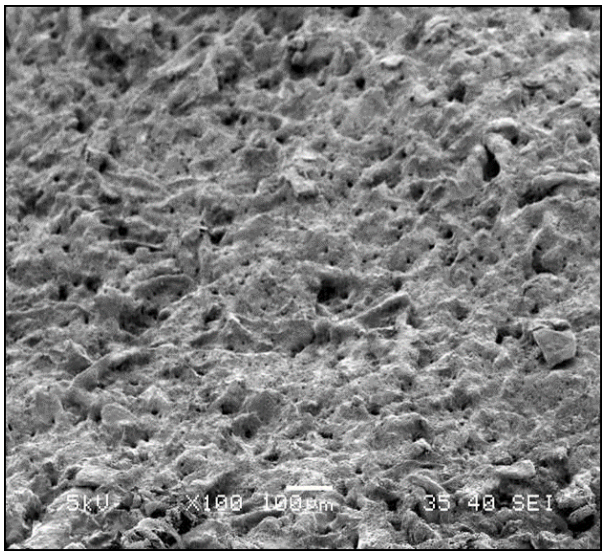



**Figure 3-8b:** SEM image SE2

## 4. Conclusion

A standard and modified screw configration was used to extrudate formulations. The double extrudated formulations demonstrated slower release profile for carbamazepine and rapid release for caffeine citrate. DSC results of extrudates confirmed the presnece of both API's in an amoprhous form, and FTIR-chemical imaging affirmed the uniform distribution of drugs in double extrudated formulations. Hot-melt extrusion utilizing a double extrusion technique assisted the modulation of drug release without changing the formulation. These results displayed the utility of double extrusion techniques for the development of fixed dose combination of drugs with different physical and chemical characteristics.

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# VITA

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